DIALOG(R)File 155:MEDLINE(R)

10930645 97282953 PMID: 9137087
Tumor therapy with an antibody-targeted **superantigen** generates a dichotomy between local and systemic immune responses.
Litton M J; Dohlsten M; Hansson J; Rosendahl A; Ohlsson L; Kalland T; Andersson J; Andersson U
Department of Immunology, Stockholm University, Sweden.
American journal of pathology (UNITED STATES) May 1997, 150 (5) p1607-18, ISSN 0002-9440 Journal Code: 0370502
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Repeated injections of a fusion protein containing the **superantigen** staphylococcal enterotoxin A (SEA) combined with a Fab fragment of a tumor-specific antibody is a highly efficient immunotherapy for mice expressing lung melanoma micrometastasis. In the present study, the systemic and local immune responses generated by this therapy were analyzed at a cellular level. Two distinct but coupled immune reactions occurred after repeated therapy. Tumor necrosis factor and macrophage inflammatory protein-1 alpha and -1 beta were immediately synthesized, in the absence of T lymphocytes, at the local tumor site in the lung. This was followed by the induction of VCAM-1 adhesion molecule expression on pulmonary vascular endothelial cells. Concurrently, the early response in the spleen was characterized by the induction of selective T cells producing interleukin (IL)-2. The primed and expanded SEA-reactive V beta 3- and V beta 11-expressing T lymphocytes accumulated to the tumor area only after Fab-SEA therapy and were not present in the lung when SEA, Fab fragment, or recombinant IL-2 was injected. The tumor-infiltrating T cells produced large amounts of interferon-gamma, but no IL-2 or Th2 type of lymphokines were detected at the tumor site in the Fab-SEA-targeted antitumor immune response. These results emphasize the necessity to investigate several sites of antigen presentation to elucidate the effects of immunotherapy.
Record Date Created: 19970520
Record Date Completed: 19970520

8/7/61 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10874333 97225980 PMID: 9122222
Genetically engineered **superantigens** as tolerable antitumor agents.
Hansson J; Ohlsson L; Persson R; Andersson G; Ilback N G; Litton M J; Kalland T; Dohlsten M
Lund Research Center, Pharmacia & Upjohn, Sweden.
Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Mar 18 1997, 94 (6) p2489-94, ISSN 0027-8424 Journal Code: 7505876
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Superantigens (SAg) are a family of bacterial and viral proteins with strong immunostimulatory properties. SAg bound to major histocompatibility complex (MHC) class II molecules activate a high frequency of T cells and represent the most potent known activators of T cells to date. To explore the use of SAg for T cell-based tumor therapy we have created a tumor-reactive SAg by engineering a fusion protein composed of a tumor-reactive mAb (C215Fab) and the bacterial SAg staphylococcal enterotoxin A (SEA). A point mutation D227A was introduced at the major MHC

class II binding site in SEA to reduce systemic toxicity. Treatment of tumor bearing mice with the Fab-SEA D227A fusion protein resulted in profound antitumor effects with a markedly reduced toxicity as compared with the wild-type Fab-SEA fusion protein. The reduced toxicity was probably due to a weak distribution of the SEA D227A fusion protein in tissues with a high MHC class II expression and low systemic cytokine levels as exhibited in mice and rabbits. The data presented demonstrate the efficacy of immunoconjugates containing a mutated SAg in directing a T cell attack against tumor cells with minimal systemic immune activation.
Record Date Created: 19970424
Record Date Completed: 19970424

8/7/62 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10064590 22008792 PMID: 12014649
T-cell immunotherapy for human MK-1-expressing tumors using a fusion protein of the **superantigen** SEA and anti-MK-1 scFv antibody.
Ueno Aruto; Arakawa Fumiko; Abe Hironori; Matsumoto Hisanobu; Kudo Toshio ; Asano Ryutaro; Tsumoto Kohei; Kumagai Izumi; Kuroki Motomu; Kuroki Masahide
Department of Biochemistry, Fukuoka University School of Medicine, Japan.
Anticancer research (Greece) Mar-Apr 2002, 22 (2A) p769-76, ISSN 0250-7005 Journal Code: 8102988
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
BACKGROUND: The bacterial **superantigen** staphylococcal enterotoxin A (SEA) is an extremely potent activator of T lymphocytes when presented on major histocompatibility complex (MHC) class II molecules. To develop a tumor-specific **superantigen** for cancer therapy, we constructed a recombinant fusion protein of SEA and the single-chain variable fragment (scFv) of the FU-MK-1 antibody, which recognizes a glycoprotein antigen (termed MK-1 antigen) present on most carcinomas. MATERIALS AND METHODS: We employed recombinant DNA techniques to fuse recombinant mutant SEA to an scFv antibody derived from FU-MK-1 and the resulting fusion protein (SEA/FUscFv) was produced by a bacterial expression system, purified with a metal-affinity column, and characterized for its MK-1-binding specificity and its antitumor activity. RESULTS: The SEA/FUscFv fusion protein retained the reactivity with MK-1-expressing tumor cells, introduced a specific cytotoxicity of lymphokine-activated killer T-cells to the tumor cells, and consequently suppressed the tumor growth in a SCID mouse xenograft model. CONCLUSION: This genetically engineered SEA/FUscFv fusion protein may serve as a potentially useful immunotherapeutic reagent for human MK-1-expressing tumors.
Record Date Created: 20020516
Record Date Completed: 20020627

8/7/63 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08925747 20214142 PMID: 10752477
Phage-selected primate antibodies fused to **superantigens** for immunotherapy of malignant melanoma.
Tordsson J M; Ohlsson L G; Abrahmsen L B; Karlstrom P J; Lando P A; Brodin T N
Active Biotech Research AB, Lund, Sweden. Jesper.Tordsson@activebiotech.com

8/7/53 (Item 1 from file: 144)
DIALOG(R)File 144:Pascal

15870169 PASCAL No.: 02-0590729
Cancer-homing toxins
Anti-Cancer Agents
NG H C; KHOO H E
CAPRANICO Giovanni, ed
Department of Biochemistry, Faculty of Medicine, National University of Singapore, 10 Kent Ridge Crescent, Singapore 119260, Singapore
Department of Biochemistry, University of Bologna, via Irnerio 48, 40126 Bologna, Italy
Journal: Current pharmaceutical design, 2002, 8 (22) 1973-1985
ISSN: 1381-6128 Availability: INIST-26320; 354000104541070030
No. of Refs.: 152 ref.
Document Type: P (Serial) ; A (Analytic)
Country of Publication: Netherlands
Language: English
Cancer-homing toxins are a group of man-made cytotoxic molecules targeting cancer cells. In the past decade they have demonstrated potential as cancer therapeutics. These molecules contain a toxin, natural or usually derivatized, connected to a cancer-homing module, such as a monoclonal antibody or growth factor or their derivatives. Various cancer-homing toxins have been designed and tested in cell-lines, animal-models and clinical trials. We review some of these data and discuss ways to better design cancer-homing toxins in the light of advances in cancer genomics, antibody-engineering techniques and computational algorithms.

8/7/54 (Item 2 from file: 144)
DIALOG(R)File 144:Pascal

12273928 PASCAL No.: 95-0504057
Superantigen-staphylococcal-enterotoxin-A-dependent and **antibody**-targeted lysis of GD SUB 2 -positive neuroblastoma cells
HOLZER U; BETHGE W; KRULL F; IHLE J; HANDGRETINGER R; REISFELD R A; DOHLSTEN M; KALLAND T; NIETHAMMER D; DANNECKER G E
Children's univ. hosp., dep. oncology/haematology, 72070 Tuebingen, Federal Republic of Germany
Journal: Cancer immunology and immunotherapy, 1995, 41 (2) 129-136
ISSN: 0340-7004 CODEN: CIIMDN Availability: INIST-16198; 354000054118640080
No. of Refs.: 35 ref.
Document Type: P (Serial) ; A (Analytic)
Country of Publication: Federal Republic of Germany
Language: English
Superantigens such as the **staphylococcal enterotoxin** A (SEA) are among the most potent T cell activators known. They bind to major histocompatibility complex (MHC) class II molecules and interact with T cells depending on their T cell receptor (TCR) V beta expression. Superantigens also induce a variety of cytokines and trigger a direct cytotoxic effect against MHC-class-II-positive target cells. In order to extend **superantigen** -dependent cell-mediated cytotoxicity (SDCC) to MHC-class-II-negative neuroblastoma cells, SEA was linked to the anti-ganglioside GD SUB 2 human/mouse chimeric **monoclonal antibody** (mAb) ch14.18. Ganglioside GD SUB 2 is expressed on most tumours of neuroectodermal origin but is expressed to a lesser extent on normal tissues. The linkage of ch14.18 to SEA was achieved either with a protein-A--SEA fusion protein or by chemical coupling. Both constructs

induced T-cell-mediated cytotoxicity towards GD SUB 2 -positive neuroblastoma cells in an effector-to-target(E :T)-ratio-and dose-dependent manner in vitro. To reducc the MHC class II affinity of SEA, a point mutation was introduced in the SEA gene (SEAm9) that resulted in 1000-fold less T cell killing of MHC-class-II-expressing cells as compared to native SEA. However, a protein-A-SEAm9 fusion protein mediated cytotoxicity similar to that of protein-A--SEA on chl4.18-coated, MHC-class-II-negative neuroblastoma cells. Taken together, these findings suggest that **superantigen**-dependent and **monoclonal-antibody**-targeted lysis may be a potent novel approach for neuroblastoma therapy.

8/7/55 (Item 3 from file: 144)
DIALOG(R)File 144:Pascal

11210547 PASCAL No.: 94-0027759
Co-stimulation with B7 and targeted **superantigen** is required for MHC class II-indendent T-cell proliferation but not cytotoxicity
LANDO P A; DOHLSTEIN M; HEDLUNG G; BRODIN T; SANSOM D; KALLAND T
Kabi Pharmacie Therapeutics, 223 62 Lund, Sweden
Journal: Immunology : (Oxford), 1993, 80 (2) 236-241
ISSN: 0019-2805 CODEN: IMMUAM Availability: INIST-1539; 354000048197370120
No. of Refs.: 38 ref.
Document Type: P (Serial) ; A (Analytic)
Country of Publication: United Kingdom
Language: English
The **superantigen Staphylococcal enterotoxin** A (SEA) **conjugated** to tumour-specific **monoclonal antibodies** (mAb) directs T cells to lyse tumour cells in the absence of major histocompatibility complex (MHC) class II. In contrast, the **conjugate** bound to MHC class II-negative tumour cells did not activate resting T cells to proliferate. The SEA-C215 mAb **conjugate**, when presented on the CA215 antigen-expressing Colo205 cells, required either signalling with CD28 mAb or CHO cells expressing the natural CD28 ligand, B7, to activate the T cells. The CD28/B7 co-stimulatory effect was further enhanced when the B7 and the tumour antigen were present on the same cell, decreasing the **superantigen** amount required for activation with a factor of 10 SUP 4

8/7/56 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11737743 99174785 PMID: 10077167
Long-term survival and complete cures of B16 melanoma-carrying animals after therapy with tumor-targeted IL-2 and SEA.
Rosendahl A; Kristensson K; Carlsson M; Skartved N J; Riesbeck K; Sogaard M; Dohlsten M
Active Biotech, Lund Research Center, Sweden. alexander.rosendahl@lrc.activebiotech.com
International journal of cancer. Journal international du cancer (UNITED STATES) Mar 31 1999, 81 (1) p156-63, ISSN 0020-7136 Journal Code: 0042124
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The bacterial **superantigen** (SAg) staphylococcal enterotoxin A (SEA) is a potent inducer of CTL activity and cytokine production in vivo. To engineer SAg for cancer immunotherapy, we genetically fused SEA to a Fab fragment of the C215 tumor-reactive antibody. Strong reduction of lung

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? ds

Set     Items   Description
S1       7128   SUPERANTIGEN AND STAPHYLOCOCC? AND (ENTEROTOXIN OR TOXIN)
S2        115   S1 AND CONJUGAT? AND (ANTIBOD? OR IMMUNOGLOB? OR MONOCLON?
                  OR IMMUNOTOXIN?)
S3         51   RD S2 (unique items)
S4        115   S1 AND CONJUGAT? AND (ANTIBOD? OR IMMUNOGLOB? OR MONOCLON?)
S5         64   IMMUNOTOXIN? AND SUPERANTIGEN?
S6         45   RD S5 (unique items)
S7         92   S3 OR S6
S8         86   RD S7 (unique items)
? s superantigen? and mutant?
          24861  SUPERANTIGEN?
        1156856  MUTANT?
      S9    1407  SUPERANTIGEN? AND MUTANT?
? rd s9
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Mycobacterium... Virus,animal, human mammary tumor...
    polypeptides of, with structural homol. to staphylococcal enterotoxins
    and streptoccccal pyrogenic exotoxins, for cancer therapy
Blood coagulation...
    procoagulant systems, enterotoxins of Staphylococcus aureus for
    activating cytokine mediators and, for treating cancer
Toxins,entero-, A... Toxins,entero-, B... Toxins,entero-, C...
Toxins,entero-, D... Toxins,entero-, E... Toxins,toxic shock, 1...
    purifn. of and cancer in rabbits treatment with, of Staphylococcus
    aureus
Streptococcus...
    pyrogenic exotoxin of, for treating cancer
Toxins,exo-...
    pyrogenic, of Streptococcus, for treating cancer
Mutagens...
    Staphylococcus aureus treatment with, in prepn. of high
    enterotoxin-producing strains, cancer treatment in relation to
Fibroblast... Immunological accessory cell... Lymphocyte...
    transfected with enterotoxin gene, for activation of T-cells and
    antitumor responses
Autoimmune disease...
    treatment of, with polypeptides homologous to staphylococcal
    enterotoxins and streptococcal pyrogenic exotoxins and superantigens
Radioelements,conjugates,compounds... Toxins,conjugates...
    with polypeptides homologous to staphylococcal enterotoxins and
    streptococcal pyrogenic exotoxins, for destroying targeted T-cells
Antigens,Mls (minor lymphocyte-stimulating)... Peptides,biological studies
... Proteins,biological studies... Proteins,specific or class, heat-shock
...
    with structural homol. to staphylococcal enterotoxins and streptococcal
    pyrogenic exotoxins, for cancer therapy
  CAS REGISTRY NUMBERS:
21645-51-2  biological studies, as adjuvant, enterotoxins of Staphylococcus
    aureus with, for cancer treatment
37259-58-8  formation of, enterotoxins of Staphylococcus aureus for
    stimulating, for cancer treatment
39391-18-9  nonsteroidal antiinflammatory compd. inhibiting synthesis of,
    toxicity of enterotoxins of Staphylococcus aureus attenuation with, in
    cancer treatment
153213-98-0  prepn. of and cancer in rabbits treatment with
15687-27-1  toxicity of enterotoxins of Staphylococcus aureus attenuation
    with, in cancer treatment
? ds

Set     Items   Description
S1       7128   SUPERANTIGEN AND STAPHYLOCOCC? AND (ENTEROTOXIN OR TOXIN)
S2        115   S1 AND CONJUGAT? AND (ANTIBOD? OR IMMUNOGLOB? OR MONOCLON?
                   OR IMMUNOTOXIN?)
S3         51   RD S2 (unique items)
S4        115   S1 AND CONJUGAT? AND (ANTIBOD? OR IMMUNOGLOB? OR MONOCLON?)
S5         64   IMMUNOTOXIN? AND SUPERANTIGEN?
S6         45   RD S5 (unique items)
S7         92   S3 OR S6
S8         86   RD S7 (unique items)
? s superantigen? and mutant?
          24861  SUPERANTIGEN?
        1156856  MUTANT?
      S9    1407  SUPERANTIGEN? AND MUTANT?
? rd s9
...examined 50 records  (50)
...examined 50 records  (100)
...examined 50 records  (150)
...examined 50 records  (200)
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125I-TSST-1 binding to MHC class II and abrogated TSST-1-induced T cell mitogenesis and TNFalpha secretion in human peripheral blood mononuclear cells. Purified GST47-64 also inhibited 125I-TSST-1 binding in a dose-dependent manner. These findings suggest that GST47-64 may have potential as a recombinant peptide vaccine or TSST-1 receptor inhibitor against TSS.

8/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11298218 BIOSIS NO.: 199800079550
Simultaneous detection of DNA synthesis and cytokine production in **staphylococcal enterotoxin** B activated CD4!+ T lymphocytes by flow cytometry.
AUTHOR: Mehta Bela A(a); Maino Vernon C
AUTHOR ADDRESS: (a)Becton Dickinson Immunocytometry Systems, 2350 Qume Drive, San Jose, CA 95131**USA
JOURNAL: Journal of Immunological Methods 208 (1):p49-59 Oct. 13, 1997
ISSN: 0022-1759
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Assessment of T cell activation has traditionally been performed by measuring proliferation as a function of 3(H)-thymidine incorporation, or secretion of cytokines from activated peripheral blood mononuclear cells (PBMC) in culture. An alternative method for detection of proliferation at the single cell level utilizes incorporation of bromodeoxyuridine (BrdU), an analog of thymidine, into cellular DNA. After appropriate fixation and permeabilization of the cells, a **monoclonal antibody** (mAb) against BrdU **conjugated** with a fluorescent dye is employed to measure by flow cytometry the incorporated BrdU. Here, we report a flow cytometric procedure which can be used for the simultaneous detection of BrdU incorporation, activation markers such as CD69 and CD25, and intracellular cytokines in T cell subsets from activated PBMC. Our observations are consistent with the proposal that cytokine synthesis and cell proliferation occur sequentially in CD4+ T cells stimulated with the **superantigen staphylococcal enterotoxin** B (SEB). The majority of cells expressing the cytokines IFN-gamma and IL-2 at 48 h appear to have undergone DNA synthesis, however all proliferating cells do not express IFN-gamma or IL-2. The methods presented in this report offer a unique approach for studying simultaneous expression of key cellular activation events in phenotypically resolved lymphocyte populations.

8/7/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11040119 BIOSIS NO.: 199799661264
Superantigen-induced lysis of melanoma cells.
AUTHOR: Krull F; Holzer U; Ihle J; Bethge W; Fierlbeck G; Kalland T; Dohlsten M; Niethammer D; Dannecker G E(a)
AUTHOR ADDRESS: (a)Dep. Oncol. Hematol., Children's Univ. Hosp., Ruemelinstrasse 23, 72070 Tuebingen**Germany
JOURNAL: Melanoma Research 7 (3):p214-222 1997
ISSN: 0960-8931
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Superantigens like the **Staphylococcus enterotoxin** A (SEA) can direct cytotoxic T lymphocytes expressing certain i cell receptor VP regions to lyse MHC class II-positive target cells. This **superantigen**-dependent cellular cytotoxicity (SDCC) has been extended to MHC class II-negative tumour cells by targeting T cells via **conjugates** of a tumour-specific **monoclonal antibody** (moAb) and a **superantigen**. In the present study the MHC class 11-negative human melanoma cell lines G361 and MaRi were tested for susceptibility to SDCC in vitro. **Antibodies** recognizing the disialoganglioside GD3 and the CD10 antigen were linked to SEA either by a recombinant protein A-SEA fusion protein or an anti-kappa moAb-SEA chemical **conjugate**. Specific lysis of melanoma cells was dose- and effector to target (E:T) cell ratio-dependent. Introduction of a point mutation into the SEA gene (producing SEAm9) in order to reduce MHC II affinity of the **superantigen**, which has already been shown to severely diminish **superantigen**-dependent binding and lysis of MHC class II-positive cells, did not influence **antibody**-targeted SDCC. Cytotoxicity was equal with both **antibodies** (anti-GD3 and anti-CD10) and independent of whether protein A-SEA, protein A-SEAm9 or anti-kappa-SEA were used.

8/7/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10758526 BIOSIS NO.: 199799379671
T-cell stimulation and cytokine release induced by **staphylococcal enterotoxin** A (SEA) and the SEAD227A mutant.
AUTHOR: Holzer U; Orlikowsky T; Zehrer C; Bethge W; Dohlsten M; Kalland T; Niethammer D; Dannecker G E(a)
AUTHOR ADDRESS: (a)Children's Univ. Hosp., Dep. Oncology/Haematology, Ruemelinstr. 23, 72070 Tuebingen**Germany
JOURNAL: Immunology 90 (1):p74-80 1997
ISSN: 0019-2805
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Previous work demonstrated that human cytotoxic T cells activated by superantigens can lyse major histocompatibility complex (MHC) class II-positive target cells as well as MHC class II-negative tumour cells coated with **conjugates** of **monoclonal antibodies** and superantigens. In order to decrease MHC class II affinity, and therefore unwanted binding of the **superantigen staphylococcal enterotoxin** A (SEA) to MHC class II molecules, a point mutation was introduced into the SEA gene. This mutation (SEAD227A) resulted in an approximately 3-log reduction of affinity to human leucocyte antigen (HLA)-DR, but cytotoxicity mediated by this mutant **superantigen** towards **antibody**-labelled tumour cells is as efficient as cytotoxicity mediated by the native **superantigen**. We therefore compared the T-cell activating potency of native and mutated SEA. Our data show that SEAD227A is 4- to 5-log less effective than native SEA when activation of resting T cells is assayed in terms of blast formation, expression of cell surface activation markers and cytokine release. Furthermore, presenting either SEA or SEAD227A to MHC class II-negative mononuclear cells by MHC class II-negative tumour cells did not result in significant blast formation of T cells, up-regulation of CD25 or cytokine release. This suggests that lysis of MHC class II-negative tumour cells is efficiently induced by **monoclonal antibody** targeted **superantigen**, while activation of resting T cells requires additional co-stimulatory signals.

methicillin-resistant Staphylococcus aureus (MRSA). Here, we analyzed the activation and the response of TSST-1-reactive Vbeta2sup + T cells in NTED patients during the acute and recovery phases and in asymptomatic infants exposed to MRSA. In the acute phase, Vbeta2+ T cells were anergic to stimulation with TSST-1 and underwent marked expansion, but by 2 months after disease onset, their numbers had declined to about 10% of the control level. Although the percentage ofVbeta2sup + T cells in the ten asymptomatic neonatal MRSA carriers was within the control range, these individuals could be divided into two groups on the basis of Vbeta2sup + T-cell activation. Vbeta2sup +CD4sup + T cells from three of these infants (Group 1) highly expressed CD45RO and were anergic to TSST-1, whereas in the other seven asymptomatic neonatal MRSA carriers (Group 2), these cells expressed CD45RO at the control level and were highly responsive to stimulation with TSST-1. The serum anti-TSST-1 IgG Ab titer was negligible in the four NTED patients in the acute phase and the three asymptomatic neonatal MRSA carriers in Group 1, but it was high in the seven asymptomatic carriers in Group 2. We suggest that maternally derived anti-TSST-1 IgGs helps to suppress T-cell activation by TSST-1 and protects infants from developing NTED.

8/7/47 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE

06705624 EMBASE No: 1996370573
Monoclonal antibody-based therapy
Von Mehren M.; Weiner L.M.
Fox Chase Cancer Center, 7701 Burholme Avenue,Philadelphia, PA 19111 United States
Current Opinion in Oncology (CURR. OPIN. ONCOL.) (United States) 1996, 8/6 (493-498)
CODEN: CUOOE ISSN: 1040-8746
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Monoclonal antibodies have been developed for cancer therapy because they specifically target tumor-related antigens. The current design of **antibodies** and delivery strategies seeks to overcome the obstacles encountered in delivering **antibodies** to their targets. Protein engineering techniques to humanize murine **antibodies** diminishes the immune response, which develops against murine **monoclonal antibodies**, allowing for multiple doses. **Antibodies** linked to vasoactive substances or **conjugated** to liposomes increase **antibody** and drug localization to tumors. Altering the sizes of **antibodies** and the methods by which they are **conjugated** to radioactive isotopes have delineated methods to increase efficacy and decrease toxicity. Tumor growth factors increasingly are being targeted by **antibody**-based therapeutics. To enhance immune activation of cytotoxic effector cells, bispecific **antibodies** and **antibodies** linked to **superantigens** are being examined. Prodrugs are being converted to their active compounds at the tumor site by **antibodies conjugated** to enzymes. Finally, intrabodies which can bind to intracellular proteins and are important for the malignant phenotype of the cell, are being developed.

8/7/48 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE

05400627 EMBASE No: 1993168726
Monoclonal antibodies and **superantigens**: A novel therapeutic

dose escalation was suspended when two patients treated in a companion repeat dose Phase I study experienced DLT at the 4 ng/kg dose level. Multiparameter analyses on all patients treated in the two companion single-dose and two-repeated-dose Phase I trials revealed that the levels of patients' pretreatment anti-SEA antibodies protected against toxicity at a given drug dose. By jointly considering weight and the baseline anti-SEA concentration in a patient, it is possible to assign a PNU-214565 dose that will induce systemic cytokine release (a surrogate test to assess for the presence of uncomplexed drug and its ability to induce systemic cellular activation) without DLT. This pharmacodynamically based dosing scheme will be tested in future repeated-dose clinical trials and will define maximally tolerated doses of this powerful new immunotherapy approach.

Record Date Created: 19981022

Record Date Completed: 19981022

8/7/58 (Item 3 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

11317450 98196941 PMID: 9537591

Repeated treatment with antibody-targeted **superantigens** strongly inhibits tumor growth.

Rosendahl A; Kristensson K; Hansson J; Ohlsson L; Kalland T; Dohlsten M

Pharmacia and Upjohn, Lund Research Center, Sweden. alexander.rosendahl@eu.pnu.com

International journal of cancer. Journal international du cancer (UNITED STATES) Apr 13 1998, 76 (2) p274-83, ISSN 0020-7136 Journal Code: 0042124

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Superantigens (SAg) are microbial proteins with the capacity to activate a large proportion of T cells. We have developed a novel approach for cancer immunotherapy by genetically fusing the SAg staphylococcal enterotoxin A (SEA) to a Fab-fragment of a tumor-specific antibody. Repeated exposure to SEA induces a state of unresponsiveness including cell deletion and functional hyporesponsiveness, i.e., anergy. In this study we have developed improved therapeutic schedules to allow repeated injections of Fab-SEA, limit development of immunological unresponsiveness and promote maximal anti-tumor response. Four daily injections of Fab-SEA to mice carrying B 16-C215 lung metastases resulted in 90-95% reduction in the number of metastases. However, the animals did retain a minimal residual tumor disease. The immune system was in a hyporesponsive state after 4 daily Fab-SEA injections, and further injections did not improve therapy. Two repeated cycles, each comprising 4 daily injections of Fab-SEA, significantly prolonged the survival and resulted in complete cure of a fraction of the animals. A rest period of 10 days between the cycles was required to mount an efficient secondary anti-tumor response. This secondary immune response was characterized by partial recovery of cytokine production i.e., interleukin-2, interferon-gamma and tumor necrosis factor-alpha. Strong CTL activity was detected in animals that had rested for 8 weeks between the 2 cycles. Interestingly, irrespective of the resting period, the CD4+ SEA-reactive T cells expanded in response to all 4 additional Fab-SEA injections both locally and in spleen. In contrast, only marginal expansion of CD8+ T cells was seen if restimulation was given within 1 month. Our data show that potent anti-tumor effector functions can be induced after repeated stimulation cycles with a SAg-monoclonal antibody fusion protein resulting in a CD4+ T cell-dependent cytokine release, prolonged survival and induction of complete cures.

Record Date Created: 19980416

Record Date Completed: 19980416

LANGUAGES: English SUMMARY LANGUAGES: English

The bacterial %%%superantigen%%% %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%% (SEA) is a highly potent activator of cytotoxic T cells when presented on MHC class II molecules of target cells. Our earlier studies showed that such SEA-directed T cells efficiently killed chronic B lymphocytic leukemia (B-CLL) cells. With the ultimate goal to replace the natural specificity of SEA for MHC class II molecules with the specificity of a monoclonal antibody (mAb), we initially made a mutated protein A-SEA (PA-SEAm) fusion protein with > 100-fold reduced binding affinity for MHC class II compared to native SEA. The fusion protein was successfully used to direct T cells to B-CLL cells coated with different B lineage specific (CD19, CD20) or associated (CD37, CD40) mAbs. The PA-SEAm protein was 10-100-fold more potent against mAb coated compared to uncoated HLA class IIsup + B-CLL cells. No correlation was seen between the amount of mAb bound to the cell surface and sensitivity to lysis. Preactivation of B-CLL cells by phorbol ester increased their sensitivity, and lysis was dependent on ICAM-1 molecules. However, no preactivation of the target cells was needed when a cocktail of two or four mAbs was used. Circulating leukemia and spleen cells were equally well killed. We conclude that the natural target specificity of SEA, MHC class II, can be reduced by mutagenesis and novel binding specificity can be introduced by linkage to tumor reactive mAbs. Our findings encourage the construction of recombinant SEA %%%mutant%%% fusion proteins for specific T cell therapy of hematopoietic tumors such as B-CLL.

7/7/52 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE
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06917215 EMBASE No: 1997201660
%%%Superantigen%%%-induced lysis of melanoma cells
Krull F.; Holzer U.; Ihle J.; Bethge W.; Fierlbeck G.; Kalland T.; Dohlsten M.; Niethammer D.; Dannecker G.E.
G.E. Dannecker, Dept. of Oncology and Hematology, Children's University Hospital, Rumelinstrasse 23, 72070 Tubingen Germany
Melanoma Research (MELANOMA RES.) (United Kingdom) 1997, 7/3 (214-222)
CODEN: MREEE ISSN: 0960-8931
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 41

%%%Superantigens%%% like the %%%Staphylococcus%%% %%%enterotoxin%%% %%%A%%% (SEA) can direct cytotoxic T lymphocytes expressing certain T cell receptor Vbeta regions to lyse MHC class II-positive target cells. This %%%superantigen%%%-dependent cellular cytotoxicity (SDCC) has been extended to MHC class II-negative tumour cells by targeting T cells via conjugates of a tumour-specific monoclonal antibody (moAb) and a %%%superantigen%%%. In the present study the MHC class II-negative human melanoma cell lines G361 and MaRI were tested for susceptibility to SDCC in vitro. Antibodies recognizing the dislaloganglioside GD3 and the CD10 antigen were linked to SEA either by a recombinant protein A SEA fusion protein or an anti-kappa moAb SEA chemical conjugate. Specific lysis of melanoma cells was dose- and effector to target (E:T) cell ratio-dependent. Introduction of s point mutation into the SEA gene (producing SEAm9) in order to reduce MHC II affinity of the %%%superantigen%%%, which has already been shown to severely diminish %%%superantigen%%%-dependent binding and lysis of MHC class II-positive cells, did not influence antibody-targeted SDCC. Cytotoxicity was equal with both antibodies (anti-GD3 and anti-CD10) and independent of whether protein A SEA, protein A SEAm9 or anti-kappa SEA were used.

7/7/53 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE
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06355385 EMBASE No: 1996013151
Isolation of HLA-DR1-(%%%staphylococcal%%% %%%enterotoxin%%% %%%A%%%)inf 2 trimers in solution
Tiedemann R.E.; Urban R.J.; Strominger J.L.; Fraser J.D.
Department of Molecular Medicine, School of Medicine, University of Auckland,Auckland New Zealand
Proceedings of the National Academy of Sciences of the United States of America (PROC. NATL. ACAD. SCI. U. S. A.) (United States) 1995, 92/26 (12156-12159)
CODEN: PNASA ISSN: 0027-8424
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Mutational studies indicate that the %%%superantigen%%% %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%% (SEA) has two separate binding sites for major histocompatibility complex (MHC) class II molecules. Direct evidence is provided here for the formation of SEA-MHC class II trimers in solution. Isoelectric focusing separated SEA-HLA-DR1 complexes into both dimers and HLA-DR1-SEAinf 2 trimers. The molar ratio of components was determined by dual isotope labeling. The SEA %%%mutant%%% SEA-F47S, L48S, Y92A, which is deficient in MHC class II alpha-chain binding, formed only dimers with HLA-DR1, whereas a second SEA %%%mutant%%% SEA-H225A, which lacks high-affinity MHC class II beta- chain binding was incapable of forming any complexes. Thus SEA binding to its MHC receptor is a two-step process involving initial beta-chain binding followed by cooperative binding of a second SEA molecule to the class II alpha chain.

7/7/54 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE
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06292807 EMBASE No: 1995330651
Cross-linking of major histocompatibility complex class II molecules by %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%% %%%superantigen%%% is a requirement for inflammatory cytokine gene expression
Mehindate K.; Thibodeau J.; Dohlsten M.; Kalland T.; Sekaly R.-P.; Mourad W.
CRRI, CHUL, 2705 Blvd. Laurier,Ste-Foy, Que. G1V-4G2 Canada
Journal of Experimental Medicine (J. EXP. MED.) (United States) 1995, 182/5 (1573-1577)
CODEN: JEMEA ISSN: 0022-1007
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

%%%Staphylococcal%%% %%%enterotoxin%%% %%%A%%% (SEA) has two distinct binding sites for major histocompatibility complex (MHC) class II molecules. The aspartic acid located at position 227 (D227) in the COOH terminus of SEA is one of the three residues involved in its interaction with the DRbeta chain, whereas the phenylalanine 47 (F47) of the NHinf 2 terminus is critical for its binding to the DRalpha chain. Upon interaction with MHC class II molecules, SEA triggers several cellular events leading to cytokine gene expression. In the present study, we have demonstrated that, contrary to wild-type SEA, simulation of the THP1 monocytic cell line with SEA mutated at position 47 (SEA(F47A)) or at position 227 (SEA(D227A)) failed to induce interleukin 1beta and tumor necrosis factor-alpha messenger RNA expression. Pretreatment of the cells with a 10-fold excess of either SEA(F47A) or SEA(D227A) prevented the increase in cytokine messenger RNA induced by wild-type SEA. However, cross-linking of SEA(F47A) or SEA(D227A) bound to MHC class II molecules with F(ab')inf 2 anti- SEA mAb leads to cytokine gene expression, whereas cross-linking with F(ab) fragments had no effect. Taken together, these results indicate that cross-linking of two MHC class II molecules by one single SEA molecule is a

encoding and in vitro expression of %%%superantigens%%% among the human
carrier isolates, only one of 414 isolates from bovine mastitis carried the genes encoding enterotoxin C and toxic shock toxin-1. These results further support the hypothesis that the bovine and human S. aureus reservoirs constitute two separate subpopulations of the species S. aureus. The results also show that these %%%superantigens%%% are generally not present in Danish S. aureus isolates from bovine mastitis, and thus play no essential role in the pathogenesis of bovine S. aureus mastitis.

11/7/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12722825 BIOSIS NO.: 200000476327
%%%Staphylococcal%%% enterotoxins.
AUTHOR: Balaban Naomi; Rasooly Avraham(a)
AUTHOR ADDRESS: (a)Center of Veterinary Medicine, US Food and Drug Administration, Washington, DC**USA
JOURNAL: International Journal of Food Microbiology 61 (1):p1-10 1 October, 2000
MEDIUM: print
ISSN: 0168-1605
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: %%%Staphylococcus%%% aureus is a major human pathogen that
produces a wide array of toxins, thus causing various types of disease symptoms. %%%Staphylococcal%%% enterotoxins (SEs), a family of nine major
serological types of heat stable enterotoxins, are a leading cause of gastroenteritis resulting from consumption of contaminated food. In addition, SEs are powerful %%%superantigens%%% that stimulate non-specific T-cell proliferation. SEs share close phylogenetic relationships, with similar structures and activities. Here we review the structure and function of each known enterotoxin.

11/7/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12121051 BIOSIS NO.: 199900415900
Involvement of enterotoxins G and I in %%%staphylococcal%%% toxic shock syndrome and %%%staphylococcal%%% scarlet fever.
AUTHOR: Jarraud Sophie; Cozon Gregoire; Vandenesch Francois; Bes Michele;
Etienne Jerome; Lina Gerard(a)
AUTHOR ADDRESS: (a)Faculte de Medecine, Laboratoire de Bacteriologie, Rue
Guillaume Paradin, 69372, Lyon Cedex 08**France
JOURNAL: Journal of Clinical Microbiology 37 (8):p2446-2449 Aug., 1999
ISSN: 0095-1137
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: We investigated the involvement of the recently described %%%staphylococcal%%% enterotoxins G and I in toxic shock syndrome. We reexamined %%%Staphylococcus%%% aureus strains isolated from patients
with menstrual and nonmenstrual toxic shock syndrome (nine cases) or %%%staphylococcal%%% scarlet fever (three cases). These strains were selected because they produced none of the toxins known to be involved in these syndromes (toxic shock syndrome toxin 1 and enterotoxins A, B, C, and D), %%%enterotoxin%%% %%%E%%% or H, or exfoliative toxin A or B, despite the fact that %%%superantigenic%%% toxins were detected in a CD69-specific flow cytometry assay measuring T-cell activation. Sets of primers specific to the enterotoxin G and I genes (seg and sei, respectively) were designed and used for PCR amplification. All of the strains were positive for seg and sei. Sequence analysis confirmed that the PCR products, corresponded to the target genes. We suggest that %%%staphylococcal%%% enterotoxins G and I may be capable of causing human
%%%staphylococcal%%% toxic shock syndrome and %%%staphylococcal%%% scarlet fever.

11/7/9 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12007285 BIOSIS NO.: 199900287804
The role of %%%superantigens%%% in vasculitis.
AUTHOR: Cohen Tervaert Jan Willem(a); Popa Eliane R; Bos Nico A
AUTHOR ADDRESS: (a)Department of Clinical Immunology, University Hospital
Groningen, Hanzeplein 1, 9713 GZ, Groning**Netherlands
JOURNAL: Current Opinion in Rheumatology 11 (1):p24-33 Jan., 1999
ISSN: 1040-8711
DOCUMENT TYPE: Literature Review
RECORD TYPE: Citation
LANGUAGE: English

11/7/10 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11141743 BIOSIS NO.: 199799762888
%%%Staphylococcal%%% enterotoxins A, D, and E structure and function, including mechanism of T-cell %%%superantigenicity%%%.
AUTHOR: Svensson L Anders(a); Schad Elinor M(a); Sundstrom Michael; Antonsson Per; Kalland Terje; Dohlsten Mikael
AUTHOR ADDRESS: (a)Lund Univ., Lund**Sweden
JOURNAL: Preparative Biochemistry & Biotechnology 27 (2-3):p111-141 1997
ISSN: 1082-6068
DOCUMENT TYPE: Literature Review
RECORD TYPE: Citation
LANGUAGE: English

11/7/11 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11023735 BIOSIS NO.: 199799644880
Retrovirally induced mouse anti-TCR monoclonals can synergize the in vitro proliferative T cell response to bacterial %%%superantigens%%%.
AUTHOR: Dehghanpisheh K; Marchalonis J J(a)
AUTHOR ADDRESS: (a)Univ. Arizona, P.O. Box 24-5049, Tucson, AZ 85724**USA
JOURNAL: Scandinavian Journal of Immunology 45 (6):p645-654 1997
ISSN: 0300-9475
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Antibodies directed against the beta chain of the T-cell receptor
(TCR) have been detected in animals and in humans in a number of distinct immune states that do not involve direct immunization with either T cells or TCR epitopes. When C57Bl/6 mice are infected experimentally with the LP-BM5 retrovirus mixture they produce increased titres of autoantibodies directed against TCR V-beta complementarity determining region I (CDR1) epitopes. Here, the authors utilized hybridoma technology to isolate monoclonal immunoglobulin (Ig)M antibodies (MoAbs) that arose at the peak
of infection. The authors characterized the binding specificity tested using synthetic peptides modelling the CDR1 segments of 24 distinct V-beta gene products and determined the VH gene usage by two such monoclonals. One binds to a restricted set of TCR V-beta CDR1 peptides, and the second reacts with approximately half of the CDR1 peptide homologues. These MoAbs are specific for T-cell receptor beta chains and do not bind to immunoglobulin light chains or to unrelated protein

Cancer immunology, immunotherapy - CII (GERMANY) Mar 2000, 48 (12) p691-702, ISSN 0340-7004 Journal Code: 8605732
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The high-molecular-weight melanoma-associated antigen, HMW-MAA, has been demonstrated to be of potential interest for diagnosis and treatment of malignant melanoma. Murine monoclonal antibodies (mAb) generated in response to different epitopes of this cell-surface molecule efficiently localise to metastatic lesions in patients with disseminated disease. In this work, phage-display-driven selection for melanoma-reactive antibodies generated HMW-MAA specificities capable of targeting bacterial **superantigens** (SAg) and cytotoxic T cells to melanoma cells. Cynomolgus monkeys were immunised with a crude suspension of metastatic melanoma. A strong serological response towards HMW-MAA demonstrated its role as an immunodominant molecule in the primate. Several clones producing monoclonal scFv antibody fragments that react with HMW-MAA were identified using melanoma cells and tissue sections for phage selection of a recombinant antibody phage library generated from lymph node mRNA. One of these scFv fragments, K305, was transferred and expressed as a Fab-SAg fusion protein and evaluated as the tumour-targeting moiety for **superantigen** -based immunotherapy. It binds with high affinity to a unique human-specific epitope on the HMW-MAA, and demonstrates more restricted cross-reactivity with normal smooth-muscle cells than previously described murine mAb. The K305 Fab was fused to the **superantigen** staphylococcal enterotoxin A (D227A) [SEA(D227A)], which had been mutated to reduce its intrinsic MHC class II binding affinity, and the fusion protein was used to demonstrate redirection of T cell cytotoxicity to melanoma cells in vitro. In mice with severe combined immunodeficiency, carrying human melanoma tumours, engraftment of human lymphoid cells followed by treatment with the K305Fab-SEA(D227A) fusion protein, induced HMW-MAA-specific tumour growth reduction. The phage-selected K305 antibody demonstrated high-affinity binding and selectivity, supporting its use for tumour therapy in conjunction with T-cell-activating **superantigens**.

Record Date Created: 20000419
Record Date Completed: 20000419

8/7/64 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08507956 95196232 PMID: 7889537
Targeting of **superantigens**.
Kalland T; Dohlsten M; Abrahmsen L; Hedlund G; Bjork P; Lando P A; Sundstedt A; Akerblom E; Lind P
Kabi Pharmacia Oncology, Lund, Sweden.
Cell biophysics (UNITED STATES) Jan-Jun 1993, 22 (1-3) p147-64, ISSN 0163-4992 Journal Code: 8002185
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The bacterial **superantigen staphylococcal enterotoxin** A (SEA) is an extremely potent activator of T lymphocytes when presented on MHC class II antigens. In order to induce T lymphocytes to reject a tumor, we substituted the specificity of SEA for MHC class II molecules with specificity for tumor cells by combining SEA with a MAb recognizing colon carcinomas. Chemical **conjugates** or recombinant fusion proteins of the MAb C215 and SEA retained excellent antigen binding properties whereas the binding to MHC class II was markedly reduced. The hybrid proteins directed SEA responsive T cells to tumors with specificity determined by the

Language: ENGLISH Document Type: ARTICLE
Abstract: Conjugates of IL-2 with the ribosome-inactivating protein gelonin were prepared using heterobifunctional reagents to link the proteins via disulfide, acid-labile, and noncleavable linkers. In each case, one protein was modified using 2-iminothiolane. The sulfhydryl groups so introduced were then reacted either with 2-nitro-5-dithiobenzoate groups or with iodoacetamido groups which had been introduced into the second protein. In the case of the acid-labile linkage, a reagent which forms a labile bond upon reaction with amino groups, 4-(iodoacetamido)-1-cyclohexene-1,2-dicarboxylic acid anhydride (its synthesis is described in this paper) was used to modify the toxin. The conjugates were separated from nonconjugated proteins by gel filtration on Sephadex G100 (SF). Each was analyzed with respect to its ribosome-inactivating activity, its ability to bind to the IL-2 receptor, and its in vitro cytotoxicity. The ribosome-inactivating activity of gelonin was unaffected by modification with 2-iminothiolane and was retained in conjugates prepared using this ragent. Modification of the toxin with 4-(iodoacetamido)-1-cyclohexene-1,2-dicarboxylic acid anhydride to form the acid-labile link drastically reduced the activity of the toxin. However, the activity of the toxin was recovered following acid treatment to release the native protein. Conjugates containing each type of linkage exhibited both specific binding and selective cytotoxicity toward cells expressing the IL-2 receptor. The most potent of these toxins, that containing the disulfide linkage, exhibited a cytotoxicity which was 2 orders of magnitude greater than that of unconjugated gelonin.

8/7/39 (Item 20 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

02893296 Genuine Article#: MN447 Number of References: 64
Title: TOXINS
Author(s): READ RJ; STEIN PE
Corporate Source: UNIV ALBERTA,DEPT MED MICROBIOL & INFECT DIS/EDMONTON T6G 2H7/ALBERTA/CANADA/; UNIV CAMBRIDGE,MRC CTR,DEPT HAEMATOL/CAMBRIDGE CB2 2QH//ENGLAND/
Journal: CURRENT OPINION IN STRUCTURAL BIOLOGY, 1993, V3, N6 (DEC), P 853-860
ISSN: 0959-440X
Language: ENGLISH Document Type: ARTICLE
Abstract: The past year has been a notable one for the structural study of toxins. Several new toxin structures have been determined, including the first example of a **superantigen**. Another first is the visualization of binding interactions with a cell-surface receptor. Unexpected structural homologies hint at unsuspected evolutionary relationships among toxin families.

8/7/40 (Item 21 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

02838534 Genuine Article#: MH756 Number of References: 44
Title: 2 SEPARATE MECHANISMS OF T-CELL CLONAL ANERGY TO MLS-1(A)
Author(s): YUI K; ISHIDA Y; KATSUMATA M; KOMORI S; CHUSED TM; ABE R
Corporate Source: UNIV PENN,DEPT PATHOL & LAB MED,DIV IMMUNOBIOL,ROOM 276,JOHN MORGAN BLDG,36TH & HAMILTON WALK/PHILADELPHIA//PA/19104; UNIV PENN,DEPT PATHOL & LAB MED,DIV IMMUNOL/PHILADELPHIA//PA/19104; NIAID,IMMUNOL LAB/ROCKVILLE//MD/20852; NCI,EXPTL IMMUNOL BRANCH/BETHESDA//MD/20892; USN,MED RES INST,IMMUNE CELL BIOL PROGRAM/BETHESDA//MD/20889

protein interacting with mAb in targeting T lymphocytes against MHC class II-negative leukemia cells while only marginally affecting normal MHC class II-positive cells, we suggest the development of SEA-mAb fusion proteins as a potential adjuvant therapy of leukemias.

8/7/12 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09069526 BIOSIS NO.: 199497077896
Preparation and characterization of **conjugates** of **monoclonal antibodies** and **staphylococcal enterotoxin** A using a new hydrophilic cross-linker.
AUTHOR: Akerblom Eva(a); Dohlsten Mikael; Bryno Charlotte; Mastej Maria; Steringer Ingrid; Hedlund Gunnar; Lando Peter; Kalland Terje
AUTHOR ADDRESS: (a)Dep. Bioorganic Chemistry, Kabi Pharmacia AB, Uppsala
JOURNAL: Bioconjugate Chemistry 4 (6):p455-466 1993
ISSN: 1043-1802
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: **Conjugates** between **monoclonal antibodies** recognizing human cancer cells and the **superantigen staphylococcal enterotoxin** A (mAb-SEA) represent a potential novel approach to tumor therapy. Such mAb-SEA **conjugates** direct T-cells to lyse colon carcinoma cells in vitro. The synthesis of mAb-SEA **conjugates** which were prepared by introducing thiol groups on SEA and iodoacetyl or maleimide groups on mAb forming a stable thioether linkage between SEA and mAb is described. A hydrophilic spacer, composed of repeated ethylene oxide units, was constructed to increase the distance between SEA and mAb, preserving biological activity of both proteins. The degree of modification of mAb with SEA was determined with SDS-PAGE. Variables influencing the composition of the **conjugates** and their effect on the tumor-cell cytotoxicity were studied and optimal conditions for the synthesis were established. Functionally active mAb-SEA **conjugates** were prepared from a panel of different mAb and T-cell-dependent cytotoxicity against several human cancer types including colon, ovarial, breast, and renal cancer was obtained. This suggests that mAb-SEA **conjugates** may be of value in the treatment of human neoplastic disease.

8/7/13 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08997105 BIOSIS NO.: 199497005475
Co-stimulation with B7 and targeted **superantigen** is required for MHC class II-independent T-cell proliferation but not cytotoxicity.
AUTHOR: Lando P A(a); Dohlsten M; Hedlund G; Brodin T; Sansom D; Kalland T
AUTHOR ADDRESS: (a)Kabi Pharm. Therapeutics, Scheelevagen 22, S-223 63 Lund **Sweden
JOURNAL: Immunology 80 (2):p236-241 1993
ISSN: 0019-2805
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The **superantigen Staphylococcal enterotoxin** A (SEA) **conjugated** to tumour-specific **monoclonal antibodies** (mAb) directs T cells to lyse tumour cells in the

absence of major histocompatibility complex (MHC) class II. In contrast, the **conjugate** bound to MHC class II-negative tumour cells did not activate resting T cells to proliferate. The SEA-C215 mAb **conjugate**, when presented on the CA215 antigen-expressing Colo205 cells, required either signalling with CD28 mAb or CHO cells expressing the natural CD28 ligand, B7, to activate the T cells. The CD28/B7 co-stimulatory effect was further enhanced when the B7 and the tumour antigen were present on the same cell, decreasing the **superantigen** amount required for activation with a factor of 10-4. No influence of B7 was seen when the single CA215 or double CA215/B7 transfectants were used as targets for **superantigen conjugate**-dependent cytotoxicity. This suggests that the low affinity T-cell receptor (TcR) interaction of **superantigen** in the absence of MHC class II antigens is sufficient for induction of cytotoxicity but requires additional CD28/B7 signalling to result in proliferation of resting T cells.

8/7/14 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08987400 BIOSIS NO.: 199396138901
In vivo tumor immunotherapy by a bacterial **superantigen**.
AUTHOR: Ochi Atsuo(a); Migita Kiyoshi; Xu Jenny; Siminovitch K
AUTHOR ADDRESS: (a)Mount Sinai Hospital Res. Inst., 600 University Ave., Toronto, ON, Can. M4Y 1X5
JOURNAL: Journal of Immunology 151 (6):p3180-3186 1993
ISSN: 0022-1767
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We have investigated the in vivo efficacy of **Staphylococcus** aureus **enterotoxin** B (SEB) coupled to tumor-specific anti-idiotypic **antibody** in redirecting T cell effector activity to the growth inhibition of B lymphoma 38C13. Incubation of 38C13 lymphoma cells with syngeneic C3H/He splenic cells and SEB-anti-Id **conjugate** was associated with between 80 and 100% growth inhibition of the tumor cells. V-beta-8+ T cells were integral for the SEB-anti-Id-induced tumor cell growth inhibition. Administration of SEB-anti-Id i.v. to mice previously inoculated with 38C13 lymphoma cells led to greater than 40% survival at 100 days compared to a mean survival of 21 days in control animals. When we compared this reagent with other targeting constructs - the anti-CD3-anti-Id and anti-TCR V-beta-8-anti-Id - these more or less effectively prevented tumor growth. However, anti-CD3-anti-Id impaired almost the entire T cell response, whereas the effects of SEB-anti-id or anti-V-beta-8-anti-Id had effects limited to V-beta-8+ T cells. Previous studies showed that in vivo administration of SEB caused a small change in V-beta-8+ T cell numbers in contrast to anti-V-beta-8 **antibody**, which depleted the entire population. These results together suggest that SEB-anti-tumor **antibody conjugates** represent a potentially powerful approach for better tumor immunotherapy.

8/7/15 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08890837 BIOSIS NO.: 199396042338
Superantigen-induced cytokines suppress growth of human colon-carcinoma cells.
AUTHOR: Dohlstein Mikael(a); Sundstedt Anette; Bjorklund Mariana; Hedlund Gunnar; Kalland Terje

appropriately adjusting doses of perfusate are also disclosed.

8/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13632852 BIOSIS NO.: 200200261673
T cell receptor (TCR) Vbeta-specific **superantigen** responses used as a model to optimize selective depletion of graft-versus-host disease (GVHD)-reacting T cells with an **immunotoxin** targeting the IL-2 receptor.
AUTHOR: Solomon Scott R(a); Tran Thao; Schindler John; Vitetta Ellen; Barrett A John(a)
AUTHOR ADDRESS: (a)Stem Cell Allotransplantation Section, NHLBI/NIH, Bethesda, MD**USA
JOURNAL: Blood 98 (11 Part 1):p852a November 16, 2001
MEDIUM: print
CONFERENCE/MEETING: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We have developed a clinical strategy to selectively eliminate alloreacting T cells from stem cell transplants (SCT) ex vivo prior to infusion, using a specific interleukin-2 receptor (IL2-r) **immunotoxin**, RFT5-SMPT-dgA (IT). This selective T cell depletion approach is being evaluated in a clinical trial to reduce GVHD following SCT. To optimize the conditions of selective depletion in vitro, we used depletion of the powerful bacterial **superantigen** (SAG) T cell response as a model. SAG bind to MHC class II molecules activating T cells in a TCR Vbeta domain-specific manner. In these experiments, peripheral blood mononuclear cells from healthy individuals were stimulated with toxic shock syndrome toxin-1 (TSST-1) SAG in serum-free medium for 72 hours causing selective activation of Vbeta2+ T cells. Flow cytometric evaluation demonstrated that the majority of Vbeta2+ activated T cells expressed IL2-r and CD71. At varying times in culture, IT was added with or without the immunopotentiator NH4Cl. Following IT exposure, responder cells were washed and restimulated with either TSST-1 or SEB (stimulating Vbeta3+, Vbeta12+, and Vbeta17+ T cells). Tritiated thymidine uptake was measured from 3-6 days after SAG stimulation. Residual proliferation against the original stimulator, TSST-1, was low (<5%), while responses to SEB were conserved between 80-100%. These experiments showed that the addition of NH4Cl at the time of IT exposure was critical for optimal depletion. Despite saturation of IL2-r sites at the time of IT exposure, maximal killing of activated cells was delayed several days. This model provides a robust method to define and optimize different methods to deplete antigen-activated T cells and should improve the development of strategies to selectively deplete GVHD-reacting T cells prior to stem cell transplantation.

8/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13470404 BIOSIS NO.: 200200099225
Mutated SEA-D227A-**conjugated antibodies** greatly enhance antitumor activity against MUC1-expressing bile duct carcinoma.
AUTHOR: Kodama Hideaki; Suzuki Masanori; Katayose Yu; Shinoda Masao; Sakurai Naoki; Takemura Shin-ichi; Yoshida Hiroshi; Saeki Hisaaki; Ichiyama Masahiko; Tsumoto Kohei; Asano Ryutaro; Kumagai Izumi; Imai

Kohzoh; Hinoda Yuji; Matsuno Seiki; Kudo Toshio(a)
AUTHOR ADDRESS: (a)Cell Resource Center for Biomedical Research, Institute of Development, Aging and Cancer, Tohoku University, Seiryomachi 4-1, Aoba-ku, Sendai, 980-8575**Japan E-Mail: j23700@gen.cc.tohoku.ac.jp
JOURNAL: Cancer Immunology Immunotherapy 50 (10):p539-548 December, 2001
MEDIUM: print
ISSN: 0340-7004
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: For the purpose of establishing a new adoptive immunotherapy for bile duct carcinoma (BDC), we have directed our attention to superantigens (SAgs), the most potent known activators of T lymphocytes. In our previous study, **staphylococcal enterotoxin** A (SEA) was **conjugated** chemically with MUSE11 mAb, which recognizes the MUC1 cancer-associated antigen, and shown to enhance the specific cytotoxic activity of T-LAK cells against MUC1-expressing BDC cells (TFK-1) in vitro and in vivo. However, it is probable that SEA might cause side-effects because of nonspecific binding to class II positive cells. In order to overcome these, we generated mutated SEA (mSEA) by changing Asp at position 227 of native SEA to Ala, which has reduced affinity to MHC class II molecules, but retains the potential for T cell activation. When mSEA-D227A was administered to rabbits to examine effects on blood pressure, 500 times more mSEA-D227A was tolerated than native SEA. This prompted us to construct a mSEA-D227A-**conjugated** mAb, reactive with MUC1. It augmented the antitumor activity of T-LAK cells significantly, and furthermore, mSEA-D227A could be **conjugated** to two bispecific **antibodies**, BsAb (anti-MUC1Xanti-CD3) and BsAb (anti-MUC1Xanti-CD28), which in combination had greater enhancing effects than mSEA-D227A-**conjugated** anti-MUC1 mAb, and combination of unconjugated BsAbs. These findings indicate a utility of mSEA-D227A-**conjugated antibodies** for targeted cancer immunotherapy.

8/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12495216 BIOSIS NO.: 200000248718
Recombinant expression and neutralizing activity of an MHC class II binding epitope of toxic shock syndrome **toxin**-1.
AUTHOR: Rubinchik Evelina; Chow Anthony W(a)
AUTHOR ADDRESS: (a)Division of Infectious Diseases, Department of Medicine, University of British Columbia, Canadian Bacterial Disease Network, and Vancouver Hospital Health Sciences Center, Vancouver, BC, V5Z 3J5**Canada
JOURNAL: Vaccine 18 (21):p2312-2320 April 28, 2000
ISSN: 0264-410X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Toxic shock syndrome (TSS) is caused by the **staphylococcal superantigen**, TSST-1. The MHC class II binding domain of TSST-1 containing a conserved sequence with other related **staphylococcal** enterotoxins, comprising TSST-1 residues 47-64 ((T(47-64)), was expressed as a fusion protein with either glutathione-S-transferase (GST47-64), filamentous phage coat protein (pIII47-64), or E. coli outer membrane porin protein (OprF47-64), or synthesized as a peptide **conjugated** to bovine serum albumin, BSA47-64. GST47-64, OprF47-64 and BSA47-64, but not pIII47-64, all induced high-titer T(47-64)-specific **antibodies** in Balb/c mice. However, only anti-GST47-64 **antibodies** inhibited

%%%staphylococcal%%%
%%%enterotoxin%%% %%%E%%% (SEE). Rat T cells reactive with MBP can
respond to SEE presented by spleen cells but not to SEE presented by LOA,
a rat T cell clone that expresses both I-A and I-E MHC class II molecules, even though LOA is much more efficient than splenic APC in the presentation of MBP. The inability of LOA to present %%%superantigen%%%
is not due to a structural difference in MHC 11 molecules between LOA and the splenic APC or to differential expression of major accessory/adhesion molecules, including CD2, CD5, CD4 and CD44, on LOA. The nonresponsiveness of SEE/LOA-induced T cells differs from anergy, in that such cells do not lose their subsequent responsiveness to either MBP or SEE. Our results demonstrate that: (i) MHC class II molecules (I-A and I-E) alone are insufficient for the activation of T cells by bacterial %%%superantigen%%%, (ii) failure to respond to antigen presented upon inappropriate APC or in inadequate doses may not necessarily represent anergy, and (iii) the quality of the T cell response towards certain ligands can be strongly influenced by the nature of the APC.

11/7/19 (Item 19 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09944256 BIOSIS NO.: 199598399174
Identification of the V-beta determinants of %%%staphylococcal%%% %%%enterotoxin%%% %%%E%%%.
BOOK TITLE: The 9th International Congress of Immunology
AUTHOR: Lamphear J G; Mollick J A; Reda K B; Rich R R
BOOK AUTHOR/EDITOR: 9TH INTERNATIONAL CONGRESS OF IMMUNOLOGY
AUTHOR ADDRESS: Baylor Coll. Med., Houston, TX**USA
p721 1995
BOOK PUBLISHER: 9th International Congress of Immunology, San Francisco,
California, USA
CONFERENCE/MEETING: Meeting Sponsored by the American Association of
Immunologists and the International Union of Immunological Societies San Francisco, California, USA July 23-29, 1995
RECORD TYPE: Citation
LANGUAGE: English

11/7/20 (Item 20 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09943539 BIOSIS NO.: 199598398457
Unresponsiveness of %%%superantigen%%%-induced CD8+ T lymphoblasts in vitro
and accessory cells.
BOOK TITLE: The 9th International Congress of Immunology
AUTHOR: Imanishi K; Yan X J; Gu Y; Li X Y; Uchiyama T
BOOK AUTHOR/EDITOR: 9TH INTERNATIONAL CONGRESS OF IMMUNOLOGY
AUTHOR ADDRESS: Tokyo Women's Med. Coll., Shinjuku-ku, Tokyo**Japan
p600 1995
BOOK PUBLISHER: 9th International Congress of Immunology, San Francisco,
California, USA
CONFERENCE/MEETING: Meeting Sponsored by the American Association of
Immunologists and the International Union of Immunological Societies San Francisco, California, USA July 23-29, 1995
RECORD TYPE: Citation
LANGUAGE: English

11/7/21 (Item 21 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09765977 BIOSIS NO.: 199598220895
Cytotoxic activity of V-beta-8+ T cells in Crohn's disease: The role of bacterial %%%superantigens%%%.
AUTHOR: Baca-Estrada M E; Wong D K H; Croitoru K(a)
AUTHOR ADDRESS: (a)Room 4H17, Intestinal Dis. Res. Program, McMaster Univ.
Med. Cent., 1200 Main St. W., Hamilton, **Canada
JOURNAL: Clinical and Experimental Immunology 99 (3):p398-403 1995
ISSN: 0009-9104
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In Crohn's disease, disease-related stimuli could alter the T cell receptor (TCR) repertoire. To examine the possibility that changes in function may occur in T cell subsets without obvious changes in expression of TCR, we analysed the TCR repertoire of cytotoxic T lymphocytes in Crohn's disease peripheral blood. Furthermore, we examined the effect of bacterial %%%superantigens%%%, %%%staphylococcal%%% enterotoxin B (SEB) and E (SEE) on the cytotoxic function of T cell subsets bearing different TCR V genes using MoAbs specific for CD3 and TCR V gene products in a redirected cytotoxicity assay. There was no difference between patients and controls in the cytotoxicity measured in concanavalin A (Con A)-stimulated peripheral blood mononuclear cells (PBMC) with anti-CD3 or with six of seven anti-TCR V gene MoAbs. However,
the cytotoxicity of V-beta-8 T cells was decreased in Crohn's disease patients. This was not due to a decrease in total or CD8+ T cells expressing V-beta-8. Furthermore, in normal subjects, PBMC stimulation with SEE and SEB selectively expanded and increased the cytotoxicity of V-beta-8 and V-beta-12 T cells, respectively. In Crohn's disease, although SEB stimulation increased the number and cytolytic function of the V-beta-12 subset, SEE stimulation failed to increase cytolytic activity of V-beta-8+ T cells in spite of the expansion of V-beta-8+ T cells. These results suggest that the changes in cytotoxic function observed in V-beta-8 T cells in Crohn's patients may reflect previous exposure to a V-beta-8-selective %%%superantigen%%%.

11/7/22 (Item 22 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09716870 BIOSIS NO.: 199598171788
Divergent effects of zinc on different bacterial pathogenic agents.
AUTHOR: Driessen Christoph; Hirv Kaimo; Kirchner Holger; Rink Lothar(a)
AUTHOR ADDRESS: (a)Inst. Immunol. Transfusion Medicie, Univ. Luebeck Sch.
Medicine, Ratzeburger Allee 160, D-23538 **Germany
JOURNAL: Journal of Infectious Diseases 171 (2):p486-489 1995
ISSN: 0022-1899
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Zinc is essential for immunologic function; therefore, it has been postulated that elevated serum levels of zinc might lead to improved immune responses. However, it is not known whether or how serum zinc levels contribute to a clinically relevant mechanism of immunologic activation. In our studies with human peripheral blood mononuclear cells and whole blood, the zinc level selectively enhanced the biologic activity of endotoxin. The combination of nonstimulatory doses of lipopolysaccharide (LPS) and nonstimulatory concentrations of zinc led to the secretion of large amounts of interleukin (IL)- 1-beta. In contrast, zinc levels specifically down-regulated monocyte activation caused by some %%%superantigens%%%, %%%staphylococcal%%% enterotoxin A and E and
Mycoplasma arthritidis-derived %%%superantigen%%%, but not toxic shock
syndrome toxin-1. This demonstrates that zinc levels control IL-1-beta secretion after both LPS and %%%superantigen%%% challenge within a clinically relevant range of concentrations. Our data suggest that the indications and contraindications for clinical zinc supplementation should be reconsidered.

11/7/23 (Item 23 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)
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09594575 BIOSIS NO.: 199598049493
Activation of T cells by %%%superantigen%%% in class II-negative mice.
AUTHOR: Avery Anne C(a); Markowitz Jay S; Grusby Michael J; Glimcher Laurie
H; Cantor Harvey(a)
AUTHOR ADDRESS: (a)Dana-Farber Cancer Inst., 44 Binney St., Boston, MA
02115**USA
JOURNAL: Journal of Immunology 153 (11):p4853-4861 1994
ISSN: 0022-1767
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The ability of the %%%staphylococcal%%% enterotoxins to stimulate
T cells has been thought to depend on their association with class II MHC products. Here, we demonstrate that a subgroup of %%%staphylococcal%%%
enterotoxins, which includes %%%staphylococcal%%% enterotoxin C and %%%staphylococcal%%% %%%enterotoxin%%% %%%E%%%, stimulates strong
MHC-independent responses, thereby resulting in T cell expansion and generation of CTL. The immunologic consequences of MHC-independent activation of T cells by %%%superantigens%%% differ from those of class II-dependent activation, inasmuch as this pathway does not result in detectable T cell deletion. These findings delineate a novel MHC-independent T cell activation pathway that leads to both clonal expansion and expression of CTL effector function in response to a subgroup of bacterial %%%superantigens%%%.

11/7/24 (Item 24 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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09488250 BIOSIS NO.: 199497496620
Costimulation of human CD4+ T lymphocytes with B7 and lymphocyte function-associated antigen-3 results in distinct cell activation profiles.
AUTHOR: Parra Eduardo; Wingren Anette Gjorloff; Hedlund Gunnar; Bjorklund
Mariana; Sjogren Hans-Olov; Kalland Terje; Sansom David; Dohlsten Mikael (a)
AUTHOR ADDRESS: (a)Wallenberg Lab., Dep. Tumor Immunol., Univ. Lund 7031,
S-220 07 Lund**Sweden
JOURNAL: Journal of Immunology 153 (6):p2479-2487 1994
ISSN: 0022-1767
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: This study describes the distinct roles of B7 and LFA-3 in the regulation of T cell responses. Activation of CD4+ T cells with Chinese hamster ovary (CHO)-DR4/B7 and CHO-DR4/LFA-3 cells that present the %%%superantigen%%% %%%staphylococcal%%% enterotoxin A resulted in significant T cell proliferation and substantial production of TNF and IFN-gamma. Strong IL-2 production was recorded in B7-costimulated, but not LFA-3-costimulated, cultures. The presence of B7 induced a more vigorous and prolonged proliferative T cell response compared with LFA-3 costimulation. In contrast, LFA-3 was more efficient than B7 in mediating cell adhesion of CD4+ T cells. Costimulation with the CHO-DR4/B7/LFA-3 triple transfectant resulted in enhanced cell adhesion, proliferation, and cytokine production compared with either DR4/B7 or DR4/LFA-3 alone.
Optimal production of IL-2 by naive and memory CD4+ T cells was seen only when cells were costimulated with B7, whereas IFN-gamma production was induced in memory cells by both LFA-3 and B7. The Jurkat T cell line responded to CHO-DR4/B7/LFA-3 in a manner similar to peripheral blood CD4+ T cells. Reverse transcriptase-PCR analysis of Jurkat cells stimulated with %%%staphylococcal%%% %%%enterotoxin%%% %%%E%%% and the different CHO transfectants revealed that the cooperative effect of B7 and LFA-3 on IL-2 production was also seen at the mRNA level. The large amounts of IL-2 produced by B7 costimulation indicate a paracrine function of the B7/CD28 pathway, whereas the LFA-3/CD2 pathway provides
strong adhesion and may facilitate autocrine T cell expansion. Combined expression of the B7 and LFA-3 molecules seems to provide an optimal Ag-presenting function that ensures strong adhesion and optimal signal transduction.

11/7/25 (Item 25 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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09440678 BIOSIS NO.: 199497449048
T cell receptor V-alpha gene usage in human T cells stimulated with SEE and SED.
AUTHOR: Liu J L; Hodara V L; Wigzell Hans(a)
AUTHOR ADDRESS: (a)Immunol. Lab. Microbiol. Tumorbiol. Cent., Karolinska Inst., 171 77 Stockholm**Sweden
JOURNAL: Scandinavian Journal of Immunology 40 (2):p269-271 1994
ISSN: 0300-9475
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: V-alpha gene usage in human T cells stimulated with SEE and SED
was investigated by using polymerase chain reaction with specific primers. V-beta-8 T cells from normal blood donors PBMC were sorted at day 5 after stimulation with SEE and analysed for TCR-V-alpha gene usage. Whole T cells stimulated with antiCD3 MoAb or SED were also analysed and
compared at different time points after stimulation. There was no biased Va gene usage found as a response to either of the two %%%superantigens%%%. These results show that V-alpha gene usage of human
T cells stimulated with SEE or SED is normal.

11/7/26 (Item 26 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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09330968 BIOSIS NO.: 199497339338
Amino and carboxyl-terminal domains of %%%staphylococcal%%% %%%enterotoxin%%% %%%E%%% mediate TCR V-beta specific interactions.
AUTHOR: Lamphear James G; Mollick Joseph A; Reda Kristin B; Rich Robert R
AUTHOR ADDRESS: Dep. Microbiol. Immunol., Baylor Coll. Med., Houston, TX
77030**USA
JOURNAL: Journal of Cellular Biochemistry Supplement 0 (18D):p366 1994
CONFERENCE/MEETING: Keystone Symposium on Lymphocyte Activation Keystone,
Colorado, USA April 10-17, 1994
ISSN: 0733-1959
RECORD TYPE: Citation
LANGUAGE: English

11/7/27 (Item 27 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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09132133 BIOSIS NO.: 199497140503
Selective anergy of V-beta-8+ T cells in human immunodeficiency virus-infected individuals.
AUTHOR: Dadaglio Gilles; Garcia Sylvie; Montagnier Luc; Gougeon Marie-Lise
(a)
AUTHOR ADDRESS: (a)Unite d'Oncologie Virale, Dep. SIDA Retrovirus, Inst.
Pasteur, 28 Rue du Dr. Roux, 75724 Paris C**France

cyclooxygenase
inhibitor indomethacin does not reverse the inhibition of TNF-alpha mRNA expression by CKS-17, suggesting that prostaglandins are not responsible for the suppressive action of CKS-17. The inhibitory effect of CKS-17 is, however, significantly blocked by a protein synthesis inhibitor cycloheximide, indicating that CKS-17 requires de novo protein synthesis to induce the suppressive activity. The mRNA stability assays using actinomycin D show that CKS-17 does not decrease the TNF-alpha mRNA stability. Nuclear run-on transcription assays further reveal that CKS-17 suppresses the TNF-alpha mRNA transcription rate. Taken together, these results suggest that the synthetic retroviral peptide CKS-17 down-regulates TNF-alpha mRNA expression through inhibition of transcriptional activation of the TNF-alpha gene, which requires de novo synthesis of a transcriptional repressor protein(s).

11/7/31 (Item 31 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08912344 BIOSIS NO.: 199396063845
Phagocytosis reduces HIV-1 production in human monocytes/macrophages infected in vitro.
AUTHOR: Piedimonte G(a); Montroni Maria; Silvestri G; Silvotti Lucia; Donatini Anna; Rossi Luigia; Borghetti A F; Magnani M
AUTHOR ADDRESS: (a)Inst. Gen. Patol., Univ. Studi, Via Gramsci 14, I-43100
Parma**Italy
JOURNAL: Archives of Virology 130 (3-4):p463-469 1993
ISSN: 0304-8608
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The addition of ingestible particles (opsonized erythrocytes or latex beads) or a phorbol ester activates monocytes - derived human macrophages (MDHM) cultured in vitro, and markedly reduces virion release
from HIV-infected MDHM as well as their ability to transmit the infection to cocultured lymphoid CD4-positive CEM cells.

11/7/32 (Item 32 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08877315 BIOSIS NO.: 199396028816
Study of activation of murine T cells with bacterial %%%superantigens%%%. In vitro induction of enhanced responses in CD4 positive T cells and of anergy in CD8 positive T cells.
AUTHOR: Yan Xiao-Jie(a); Li Xiao-Yu; Imanishi Ken'ichi; Kumazawa Yoshio; Uchiyama Takehiko
AUTHOR ADDRESS: (a)Dep. Microbiol. Immunol., Tokyo Women's Med. Coll., 8-1
Kawada-cho, Chinjuku-ku, Tokyo 162**Japan
JOURNAL: Journal of Immunology 150 (9):p3873-3881 1993
ISSN: 0022-1767
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Primary and secondary responses of murine CD4+ T cells and CD8+ T
cells upon stimulation with %%%staphylococcal%%% %%%enterotoxin%%% %%%E%%% (SEE) bearing %%%superantigenic%%% properties were examined. Both
isolated C57BL/6 splenic CD4+ T cells and CD8+ T cells proliferated and produced IL-2 and IFN-gamma upon stimulation with SEE in substantial levels. The amounts of IL-2 were greater in CD4+ T cells and those of IFN-gamma were somewhat greater in CD8+ T cells. SEE-induced CD4+ T lymphoblasts, larger parts of which bore the V-beta-11 element in their TCR, proliferated, produced IL-2 and IFN-gamma, and showed toxin-dependent cytotoxicity in substantial levels upon restimulation with SEE. By contrast, SEE-induced CD8+ T lymphoblasts, the larger part of which bore the V-beta-11 element, did not show the first two of the three responses at all upon restimulation with SEE, whereas these cells showed greater cytotoxicity. The CD8+ T lymphoblasts did not suppress the
reactivity of the CD4+ T lymphoblasts. Both SEE-induced CD4+ T lymphoblasts and CD8+ T lymphoblasts proliferated and produced IL-2 and IFN-gamma in comparable levels upon stimulation with rIL-2 or mAb to CD3
or V-beta-11.

11/7/33 (Item 33 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08853531 BIOSIS NO.: 199396005032
T cell response to %%%staphylococcal%%% %%%superantigens%%% by asymptomatic
HIV-infected individuals exhibits selective changes in T cell receptor V-beta-chain usage.
AUTHOR: Bisset Leslie R(a); Opravil Milos; Ludwig Elisabeth; Fierz Walter
AUTHOR ADDRESS: (a)Section Clinical Immunology, Dep. Internal Med., University Hosp., 8044 Zurich**Switzerland
JOURNAL: AIDS Research and Human Retroviruses 9 (3):p241-246 1993
ISSN: 0889-2229
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Recognition that the murine mammary tumor C-type retrovirus and
the replication-defective murine leukemia virus have "%%%superantigen%%%"
properties raises the specter that human immunodeficiency virus might also generate T cell impairment and destruction as a result of inherent %%%superantigen%%% properties. The observation that individuals with AIDS
lack the expression of several T cell receptor V-beta-chain genes lends support to this hypothesis. %%%Staphylococcal%%% exotoxins represent another class of %%%superantigen%%% with a similar ability to stimulate large numbers of T cells bearing specific T cell receptor V-beta-chain types. To examine the hypothesis that T cells from HIV-infected individuals may be exposed to a %%%superantigen%%% during the infection process, we have compared the ability of T cells from asymptomatic HIV-infected donors and healthy donors to respond to stimulation with several known staphyloccal exotoxin %%%superantigens%%%. Following in vitro stimulation with %%%staphylococcal%%% enterotoxin D and %%%staphylococcal%%% %%%enterotoxin%%% %%%E%%%, asymptomatic HIV-infected
individuals responded with a significantly different T cell receptor V-beta-chain usage to that observed for healthy individuals. This skewed V-beta-chain usage is likely to reflect preferential conditioning of T cells bearing specific V-beta-chains as a result of HIV infection, supporting the hypothesis of %%%superantigen%%% involvement early in the
course of infection.

11/7/34 (Item 34 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08796616 BIOSIS NO.: 199395085967
Localization of a site on bacterial %%%superantigens%%% that determines T
cell receptor beta chain specificity.
AUTHOR: Mollick Joseph A; McMasters Richard L; Grossman Douglas; Rich Robert R(a)
AUTHOR ADDRESS: (a)Immunol. Sect., M929, Baylor Coll. Med., One Baylor Plaza, Houston, TX 77030**USA
JOURNAL: Journal of Experimental Medicine 177 (2):p283-293 1993
ISSN: 0022-1007
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A defining characteristic of %%%superantigens%%% is their ability

to stimulate T cells based predominantly on the type of variable segment of the T cell receptor (TCR) beta chain (V-beta). The V-beta specificity of these toxins most likely results from direct contact between the toxin and the TCR, although the low affinity nature of this binding has prevented direct assessment of this interaction. To identify important functional sites on the toxin, we created chimeric enterotoxin genes between %%%staphylococcal%%% enterotoxins A and E (SEA and SEE) and tested the V-beta specificity of the chimeric toxins. This approach allowed us to identify three amino acid residues in the extreme COOH terminus of these toxins that are largely responsible for their ability to stimulate either human V-beta-5- or V-beta-8-bearing T cells, or mouse V-beta-3 or V-beta-11. We also found that residues in the NH-2 terminus were required for wild-type levels of V-beta-specific T cell activation, suggesting that the NH-2 and COOH ends of these %%%superantigens%%% may come together to form the full TCR V-beta contact site. SEA and SEE also differ with respect to their class II binding characteristics. Using the same chimeric molecules, we demonstrate that the first third of the molecule controls the class II binding phenotype. These data lead us to propose that for SEA and SEE, and perhaps for all bacterial-derived %%%superantigens%%%, the COOH and NH-2 termini together form the contact sites for the TCR and therefore largely determine the V-beta specificity of the toxin, while the NH-2 terminus alone binds major histocompatibility complex class II molecules. The predominant role of the COOH terminus of bacterial %%%superantigens%%% in determining V-beta specificity resembles current models being proposed for virally encoded %%%superantigens%%%, suggesting that these molecules may demonstrate some structural relationship not seen at the amino acid level.

11/7/35 (Item 35 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08291049 BIOSIS NO.: 000094062347
ZINC REGULATES THE FUNCTION OF TWO %%%SUPERANTIGENS%%%
AUTHOR: FRASER J D; URBAN R G; STROMINGER J L; ROBINSON H
AUTHOR ADDRESS: DEP. MOL. MED., UNIVERSITY OF AUCKLAND MED. SCH., AUCKLAND, NEW ZEALAND.
JOURNAL: PROC NATL ACAD SCI U S A 89 (12). 1992. 5507-5511. 1992
FULL JOURNAL NAME: Proceedings of the National Academy of Sciences of the United States of America
CODEN: PNASA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: %%%Staphylococcal%%% enterotoxins bind with high affinity to class II major histocompatibility complex proteins and subsequently stimulate large numbers of T cells via the V.beta. portion of the T-cell receptor. Binding of enterotoxin A and %%%enterotoxin%%% %%%E%%% to HLA-DR was completely abolished by low levels of EDTA, whereas binding of toxic shock toxin was unaffected. Addition of Zn2+ to as little as 2 .mu.M excess over EDTA completely reconstituted binding, but Ca2+, Mg2+, Cu2+, Fe2+, and Mn2+ had no effect. The dissociation constant (Kd) of 65Zn2+ binding to a single site on purified enterotoxin A was 2 .mu.M, and addition of purified HLA-DR1 did not alter the Kd, indicating that the binding site was exclusive to enterotoxin A. In the presence of saturating levels of zinc the Kd for enterotoxin A binding to purified HLA-DR1 was 25 nM. Thus, zinc binding is an essential first step in the formation of the major histocompatibility complex binding domain of at least two bacterial %%%superantigens%%%. Given the measured Kd of zinc binding to enterotoxin A, serum levels of free zinc (0.2-1.0 .mu.M) may well regulate the toxic sequelae by these two %%%superantigens%%%.

11/7/36 (Item 36 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08136481 BIOSIS NO.: 000093123629
PROTECTION FROM EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS BY APPLICATION OF A BACTERIAL %%%SUPERANTIGEN%%%
AUTHOR: ROTT O; WEKERLE H; FLEISCHER B
AUTHOR ADDRESS: FIRST DEP. MED., UNIV. MAINZ, MAINZ, GER.
JOURNAL: INT IMMUNOL 4 (3). 1992. 347-353. 1992
CODEN: INIME
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Certain bacterial and viral T cell stimulating proteins (' %%%superantigens%%%') are known to be very potent activators of T cells with certain V.beta. receptors. When applied in vivo these molecules induce anergy in those T cells responding to them. In this study we have investigated the influence of %%%staphylococcal%%% enterotoxins (SE) on myelin basic protein (MBP)-specific T cells in Lewis rats. As MBP-specific T cells in rats belong exclusively to the V.beta.8.2+ CD4+ subset, the induction of experimental allergic encephalomyelitis (EAE) allows for an estimation of the functional state of the respective V.beta.-bearing T cells after enterotoxin-induced activation. In vitro, various MBP-specific T cell lines showed a strong selective proliferative response to %%%staphylococcal%%% %%%enterotoxin%%% %%%E%%% (SEE) but not to other SE. The in vitro activation by SEE induced encephalitogenic potential in these cells. After application of SEE to Lewis rats the susceptibility to induction of EAE was completely abrogated. Such SEE-treated with MBP-challenged rats did not exhibit any signs of disease and their T cells did not respond to MBP in proliferation tests. This abrogation of EAE was only found with a %%%superantigen%%% capable of interacting specifically with V.beta.8.2+ T cells. %%%Superantigen%%% -mediated induction of unresponsiveness may have relevance for the analysis of pathogenetic mechanisms and for therapeutic considerations in certain T cell-mediated autoimmune diseases.

11/7/37 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

08801881 Genuine Article#: 331HG Number of References: 17
Title: Comparison of serum specific IgE antibodies to %%%staphylococcal%%% enterotoxins between atopic children with and without atopic dermatitis
Author(s): Lin YT; Yang YH; Hwang YW; Tsai MJ; Tsao PN; Chiang BL (REPRINT) ; Shau WY; Wang LF
Corporate Source: NATL TAIWAN UNIV HOSP,DEPT PEDIAT, 7 CHUNG SHAN S RD/NEW YORK//NY/10002 (REPRINT); NATL TAIWAN UNIV HOSP,DEPT PEDIAT/NEW YORK//NY/10002; NATL TAIWAN UNIV,COLL MED, GRAD INST CLIN MED/TAIPEI 10018//TAIWAN/; NATL TAIWAN UNIV HOSP,DEPT DERMATOL/TAIPEI//TAIWAN/
Journal: ALLERGY, 2000, V55, N7 (JUL), P641-646
ISSN: 0105-4538 Publication date: 20000700
Publisher: MUNKSGAARD INT PUBL LTD, 35 NORRE SOGADE, PO BOX 2148, DK-1016 COPENHAGEN, DENMARK
Language: English Document Type: ARTICLE
Abstract: Background: The skin of patients with atopic dermatitis (AD) exhibits a striking susceptibility to colonization and infection by, %%%Staphylococcus%%% aureus. The exotoxins secreted by S. aureus can act as %%%superantigens%%% and classic allergens, inducing the production of functionally relevant specific IgE antibodies. The aim of this study was to compare the levels and positive rates of serum %%%staphylococcal%%% enterotoxin A (SEA)- and %%%staphylococcal%%% %%%enterotoxin%%% %%%E%%% (SEB)-specific IgE between atopic children with and without AD.

Methods: Sixty children with AD, 55 children with respiratory

transcriptional level differs among mouse strains, suggesting clonal deletion. In the present study, we reconstituted by transfection functional TcR using the V beta 20 segment with different Va segments and studied the action of %%%superantigen%%% toxins. The V beta 20-transfectant T cells are activated by %%%staphylococcal%%% enterotoxins A and E (SEA and SEE) but not by the other tested toxins. The activation is dependent on the presence of cells expressing major histocompatibility complex class II molecules. Different HLA DR alleles can present the bacterial toxins, establishing that they interact with TcRV beta 20 as %%%superantigens%%%. Moreover, the Ver domain associated with the V beta 20 domain has an influence on the response to these toxins. The fact that V beta 20 is recognized by SEA and SEE, although both toxins are known to interact with different sets of V beta, suggests the presence of different TcR binding sites on the toxins.

11/7/44 (Item 8 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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04803699 Genuine Article#: UH861 Number of References: 62
Title: T-CELL REPERTOIRE AND INFLAMMATORY BOWEL-DISEASE
Author(s): CROITORU K; WONG DKH; BACAESTRADA ME
Corporate Source: MCMASTER UNIV,DEPT MED,IDRP,1200 MAIN ST W,ROOM4W8/HAMILTON/ON L8N 3Z5/CANADA/
Journal: CANADIAN JOURNAL OF GASTROENTEROLOGY, 1996, V10, N2 (MAR-APR), P 110-114
ISSN: 0835-7900
Language: ENGLISH Document Type: ARTICLE
Abstract: The diversity of the T cell receptor repertoire is generated through rearrangement of the variable, junctional and constant region genes. Selection processes in the thymus and periphery serve to eliminate self-reacting T cells, thereby preventing autoimmune disease. The possibility that inflammatory bowel disease (IBD) is an autoimmune disease has led to the search for an auto-antigen. In addition, studies are exploring the T cell receptor repertoire in IBD patients for changes that may provide clues regarding etiopathogenesis. Using monoclonal antibodies to T cell receptor variable-gene products or polymerase chain reaction analysis of variable-gene mRNA expression, the mucosal T cell repertoire has been examined in humans. The intestinal intraepithelial lymphocytes show a significant degree of oligoclonal expansion that may represent local antigen exposure or unique selection processes. This is in keeping with studies that show that murine intestinal intraepithelial lymphocytes undergo positive and possible negative selection independent of the thymus. In the inflamed human gut, shifts in the T cell receptor repertoire may also reflect recruitment of peripheral T cells to the gut. In one study, a subset of Crohn's disease patients was shown to have an increase in the proportion of variable beta 8 peripheral blood lymphocyte and mesenteric lymph node cells, suggesting a %%%superantigen%%% effect. Th authors hypothesized that changes in the functional T cell receptor repertoire can also occur which might be independent of changes in the distribution of T cells expressing variable beta T cell receptors. In fact, the authors have shown there is a selective decrease in the cytotoxic function of peripheral variable beta 8 T cells in Crohn's disease. Furthermore, stimulation with the variable beta 8 selective bacterial enterotoxin %%%staphylococcal%%% %%%enterotoxin%%% %%%E%%% failed to increase the cytotoxic function in this subset of Crohn's disease patients compared with controls. This suggests that in Crohn's disease, variable beta 8 T cells have undergone an alteration in function that may reflect previous exposure to a %%%superantigen%%% -like stimulus. The relationship to the etiology and pathogenesis of IBD remains to be defined.

11/7/45 (Item 9 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2003 Inst for Sci Info. All rts. reserv.

04075534 Genuine Article#: RC440 Number of References: 8
Title: LETHALLY IRRADIATED NORMAL STRAINS OF MICE RADIOPROTECTED WITH SCID BONE-MARROW DEVELOP SENSITIVITY TO LOW-DOSES OF %%%STAPHYLOCOCCAL%%%-%%%ENTEROTOXIN%%%-%%%E%%%
Author(s): ABOUDPIRAK E; LUBIN I; PIRAK ME; CANAAN A; LOWELL GH; REISNER Y
Corporate Source: WEIZMANN INST SCI,DEPT MEMBRANE RES & BIOPHYS/IL-76100 REHOVOT//ISRAEL/; WEIZMANN INST SCI,DEPT MEMBRANE RES & BIOPHYS/IL-76100 REHOVOT//ISRAEL/; WEIZMANN INST SCI,DEPT CHEM IMMUNOL/IL-76100 REHOVOT//ISRAEL/; WALTER REED ARMY INST RES/WASHINGTON//DC/00000
Journal: IMMUNOLOGY LETTERS, 1995, V46, N1-2 (MAY), P9-14
ISSN: 0165-2478
Language: ENGLISH Document Type: ARTICLE
Abstract: Normal strains of mice are rendered sensitive to small amounts (3-10 mu g) of %%%staphylococcal%%% enterotoxin B (SEB) by transplanting bone marrow cells of SCID donor mice to lethally irradiated recipients. Four to 12 weeks post-transplantation, SEB induces 56-100% lethality. Transplantation of normal mouse bone marrow cells, either alone or with the SCID mouse selected bone marrow cells, does not confer SEB sensitivity. These data imply that either irradiation ablates certain cell population(s), that confer resistance to SEB in normal mice (populations that are absent in the SCID donor mice) or that the donor cells selectively repopulate recipients with SEB-sensitive cells. This model will help elucidate the cells, cytokines and the SEB peptide fragments responsible for SEB toxicity and will be useful in identifying promising vaccine candidates and in developing preventive medicines to protect against this potent toxin.

11/7/46 (Item 10 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2003 Inst for Sci Info. All rts. reserv.

02140700 Genuine Article#: KE652 Number of References: 26
Title: 2 ADJACENT RESIDUES IN %%%STAPHYLOCOCCAL%%% ENTEROTOXIN-A AND %%%ENTEROTOXIN%%%-%%%E%%% DETERMINE T-CELL RECEPTOR V-BETA-SPECIFICITY
Author(s): HUDSON KR; ROBINSON H; FRASER JD
Corporate Source: UNIV AUCKLAND,SCH MED,DEPT MOLEC MED,PRIVATE BAG 02019/AUCKLAND//NEW ZEALAND/; UNIV AUCKLAND,SCH MED,DEPT MOLEC MED,PRIVATE BAG 02019/AUCKLAND//NEW ZEALAND/
Journal: JOURNAL OF EXPERIMENTAL MEDICINE, 1993, V177, N1 (JAN 1), P175-184
ISSN: 0022-1007
Language: ENGLISH Document Type: ARTICLE
Abstract: The T cell receptor (TCR) Vbeta-determining region of two bacterial %%%superantigens%%%, %%%staphylococcal%%% enterotoxin A (SEA) and SEE, has been mapped to the COOH-terminal region of SEA and SEE using a panel of recombinant SEA/SEE hybrids. Total TCR Vbeta mRNA enrichment in human peripheral blood T cell cultures was determined by a navel single-tube amplification technique using a redundant Vbeta-specific primer. SEA routinely enriched mRNA coding for hVbeta1.1, 5.3, 6.3, 6.4, 6.9, 7.3, 7.4, and 9.1, while SEE, which is 83% homologous to SEA, enriched hVbeta5.1, 6.3, 6.4, 6.9, and 8.1 mRNA. Exchanging residues 206 and 207 was sufficient to convert in toto the TCR Vbeta response of human peripheral T lymphocytes. In addition, an SEA-reactive murine T cell line, SO3 (mVbeta17), unresponsive to wild-type SEE responded to SEE-S206N207, while an SEE-specific human T cell line, Jurkat (hVbeta8.1), unresponsive to SEA was stimulated strongly by SEA-P206D207. Exchanging all other regions of SEA and SEE except residues 206 and 207 did little to change the Vbeta response. Thus, the Vbeta binding region appears to be a stable, discrete domain localized within the COOH-terminal region that is largely unaffected by the considerable amino acid variability between SEA and SEE. This region may interact directly with TCR Vbeta.

11/7/47 (Item 11 from file: 34)

Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Proliferation of murine T lymphocytes in blood, lymph nodes, and spleen was studied in four in vivo stimulation systems, using BrdU pulse-labeling of DNA-synthesizing cells. The T cell response to the %%%superantigen%%% %%%Staphylococcus%%% enterotoxin B (SEB) was studied in detail. Vbeta8+ T cells showed a peak of DNA synthesis 16-24 h after SEB injection, and the percentage of BrdU+ CD4 and CD8 T cells was higher in blood than in lymph nodes and spleen. DNA synthesis was preceded by massive migration of Vbeta8+ cells from blood to lymphoid organs, in which the early activation marker CD69 was first up-regulated. SEB-nonspecific Vbeta6+ cells showed minimal stimulation but, when cycling, also expressed a high level of CD69. The other systems studied were injection of the IFN-gamma inducer polyinosinic:polycytidylic acid, infection by the BM5 variants of murine leukemia virus (the causative agent of murine AIDS), and T cell expansion after transfer of normal bone marrow and lymph node cells into recombinase-activating gene-2-deficient mice. In each case, a peak of T cell proliferation was observed in blood. These data demonstrate the extensive redistribution of cycling T cells in the first few hours after activation. Kinetic studies of blood lymphocyte status appear crucial for understanding primary immune responses because cycling and redistributing T lymphocytes are enriched in the circulating compartment.
Record Date Created: 19990520
Record Date Completed: 19990520

11/7/58 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2003 The Dialog Corp. All rts. reserv.

11643503 99077502 PMID: 9862666
Nuclear factor of activated T cells and AP-1 are insufficient for IL-2 promoter activation: requirement for CD28 up-regulation of RE/AP.
Shapiro V S; Mollenauer M N; Weiss A
Department of Medicine, University of California, San Francisco 94143, USA.
Journal of immunology (Baltimore, Md. - 1950) (UNITED STATES) Dec 15 1998, 161 (12) p6455-8, ISSN 0022-1767 Journal Code: 2985117R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
IL-2 gene transcription in T cells requires both TCR and costimulatory signals. IL-2 promoter activation in Jurkat T cells stimulated with %%%superantigen%%% presented by Raji B cells requires CD28 activation. The addition of rCTLA4Ig, which blocks CD28 binding to its ligand, to the cultures decreased IL-2 promoter activation by >80%. Interestingly, CTLA4Ig did not significantly inhibit the activation of either NF of activated T cells (NFAT) or AP-1 reporters. Therefore, activation of NFAT and AP-1 is insufficient for IL-2 promoter activation. In contrast, an RE/AP reporter was blocked by CTLA4Ig by >90%. Thus, the requirement for CD28 in IL-2 promoter activation appears to be due to RE/AP and not the NFAT or AP-1 sites. In addition, these data suggest that transcriptional activation of RE/AP is not mediated by NFAT, because activation of a NFAT reporter is not affected by the addition of CTLA4Ig.
Record Date Created: 19990122
Record Date Completed: 19990122

11/7/59 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2003 The Dialog Corp. All rts. reserv.

11317683 98197176 PMID: 9536114
Synovial fibroblasts as target cells for %%%staphylococcal%%% enterotoxin-induced T-cell cytotoxicity.
Kraft M; Filsinger S; Kramer K L; Kabelitz D; Hansch G M; Schoels M
Institute of Immunology, University of Heidelberg, Germany.
Immunology (ENGLAND) Jan 1998, 93 (1) p20-5, ISSN 0019-2805 Journal Code: 0374672
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Rheumatoid arthritis (RA) is a chronic autoimmune disease of unknown aetiology. Recently, %%%superantigens%%% have been implied in the pathogenesis of RA. %%%Superantigens%%% activate a large fraction of T cells leading to the production of cytokines and proliferation. In addition, %%%superantigens%%% direct cellular cytotoxicity towards major histocompatibility complex (MHC) class II-expressing cells. There is now increasing evidence that cytotoxic T cells may be involved in the pathogenesis of RA. In the inflamed synovia class II-positive synovial fibroblasts (SFC) are found. In the present study it was tested whether MHC class II-positive SFC serve as target cells for %%%superantigen%%%-induced cellular cytotoxicity. SFC were stimulated with interferon-gamma to express class II antigens, then they were cultivated in the presence of CD4-positive T cells with or without %%%staphylococcal%%% enterotoxins (SE). Cytotoxicity of T cells was measured as release of lactate dehydrogenase from SFC. Specific cytotoxicity was only found in the presence of class II-positive SFC depending on the dose of SE. Maximum lysis was seen after 20 hr. T-cell cytotoxicity was inhibited by antibodies to MHC class II antigens. The data suggest that class II-positive SFC not only function as accessory cells for SE-mediated T-cell proliferation and interleukin-2 production but may also be the targets of %%%superantigen%%% -mediated cellular cytotoxicity.
Record Date Created: 19980410
Record Date Completed: 19980410

11/7/60 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2003 The Dialog Corp. All rts. reserv.

10920009 97272141 PMID: 9126986
Functional characterization of the interaction between the %%%superantigen%%% %%%staphylococcal%%% enterotoxin A and the TCR.
Antonsson P; Wingren A G; Hansson J; Kalland T; Varga M; Dohlsten M
Pharmacia and Upjohn, Lund Research Center, Sweden. per.antonsson@eu.pnu.com
Journal of immunology (Baltimore, Md. - 1950) (UNITED STATES) May 1 1997, 158 (9) p4245-51, ISSN 0022-1767 Journal Code: 2985117R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
In this report, we show that despite an overall amino acid residue identity of more than 80% between the %%%staphylococcal%%% enterotoxins (SE) A and E, these proteins markedly differ in their absolute requirement for the MHC class II during T cell activation. The %%%superantigens%%% were produced as C215Fab-SE fusion proteins and analyzed for their ability to activate T cells in a MHC class II-independent manner, using C215 Ag expressing cell lines as pseudo super-APCs. C215Fab-SEA, but not C215Fab-SEE, induced T cell cytotoxicity and proliferation in these MHC class II-independent systems. Introduction of a region from SEA, comprising amino acids 20-27, to SEE transferred the ability to engage T cells in the absence of MHC class II. Analysis of the Vbeta specificity of the chimeric SEA/SEE molecules and a panel of SEA mutants demonstrated that the site for TCR interaction covers the edge surrounding the shallow cavity on top of the SEA molecule.

alpha-region to either aid or hinder the interaction with class II predicts its frequency in a %%%superantigen%%%-responding population of T cells.
Record Date Created: 19960117
Record Date Completed: 19960117

11/7/64 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2003 The Dialog Corp. All rts. reserv.

09256292 20571762 PMID: 11122456
Polymorphonuclear neutrophils as accessory cells for T-cell activation: major histocompatibility complex class II restricted antigen-dependent induction of T-cell proliferation.
Radsak M; Iking-Konert C; Stegmaier S; Andrassy K; Hansch G M
Institut fur Immunologie und Medizinische Klinik der Universitat Heidelberg, Heidelberg, Germany.
Immunology (ENGLAND) Dec 2000, 101 (4) p521-30, ISSN 0019-2805 Journal Code: 0374672
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Polymophonuclear cells (PMN) of healthy donors do not express major histocompatibility complex (MHC) class II antigens or the T-cell costimulatory molecules CD80 or CD86. Expression of these receptors, however, is seen in patients with chronic inflammatory diseases. We now report that, by culturing PMN of healthy donors with autologous serum, interferon-gamma (IFN-gamma) and granulocyte-macrophage colony-stimulating
factor (GM-CSF), de novo synthesis of MHC class II, CD80 and CD86 could be
induced. MHC class II-positive PMN acquired the capacity to present %%%staphylococcus%%% enterotoxin to peripheral T cells, apparent as induction of interleukin-2 (IL-2) synthesis and proliferation of the T cells. Moreover, the PMN also processed tetanus toxoid (TT) and induced proliferation of TT-specific T cells in a MHC class II-restricted manner. Taken together, these data indicate that PMN can be activated to function as accessory cells for T-cell activation.
Record Date Created: 20001229
Record Date Completed: 20010111

11/7/65 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2003 The Dialog Corp. All rts. reserv.

08963023 20253148 PMID: 10792500
Fibronectin synthesis by activated T lymphocytes: up-regulation of a surface-associated isoform with signalling function.
Wagner C; Burger A; Radsak M; Blum S; Hug F; Hansch G M
Institut fur Immunologie, Universitat Heidelberg, Heidelberg, Germany.
Immunology (ENGLAND) Apr 2000, 99 (4) p532-9, ISSN 0019-2805 Journal Code: 0374672
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Fibronectin (FN) is a major constituent of the extracellular matrix. We now provide evidence for a surface-associated isoform of FN that is synthesized by T cells upon activation. The T-cell-derived FN has an unusual splice pattern: an additional domain, EDB, is produced whereas sequences within another domain, IIICS, are spliced out. CS1, the binding domain for very late antigen-4 (VLA-4), however, is still generated. To study the potential function of surface-associated FN its synthesis was down-regulated by an antisense oligonucleotide, then proliferation of T cells was induced by cross-linked anti-CD3. Proliferation was reduced as was expression of CD25. Moreover, when T cells were cultured in high density, the synthetic peptide QILDVPST, corresponding to CS1, inhibited proliferation, as did antibodies to VLA-4. We propose that surface-associated FN is a ligand for VLA-4, which by binding to VLA-4 on an adjacent cell, provides a costimulatory signal, thus sustaining T-cell proliferation.
Record Date Created: 20000531
Record Date Completed: 20000531

11/7/66 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2003 The Dialog Corp. All rts. reserv.

08704555 95393160 PMID: 7664046
Crystal and solution structures of %%%superantigenic%%% %%%staphylococcal%%% enterotoxins compared.
Singh B R; Fu F N; Ledoux D N
Nature structural biology (UNITED STATES) Jun 1994, 1 (6) p358-60, ISSN 1072-8368 Journal Code: 9421566
Document type: Letter
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Record Date Created: 19951010
Record Date Completed: 19951010

11/7/67 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2003 The Dialog Corp. All rts. reserv.

08581974 95270276 PMID: 7751004
Zinc regulates cytokine induction by %%%superantigens%%% and lipopolysaccharide.
Driessen C; Hirv K; Kirchner H; Rink L
Institute of Immunology and Transfusion Medicine, University of Lubeck School of Medicine, Germany.
Immunology (ENGLAND) Feb 1995, 84 (2) p272-7, ISSN 0019-2805 Journal Code: 0374672
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Zinc is known to be greatly involved in the regulation of immune functions. Pharmacological zinc supplementation, leading to serum zinc concentrations of more than 0.025 mM, has often been suggested to improve
immune responses. However, the exact influence of elevated zinc level on immune functions has not yet been investigated. We found that zinc level selectively enhances cytokine induction by lipopolysaccharide (LPS) in a concentration-dependent fashion: as little as 0.0125 mM supplemental zinc led to nearly 50% elevated interleukin-1 beta (IL-1 beta) levels both in polymorphonuclear cells (PBMC) and whole-blood cultures. The secretion of interferon-gamma (IFN-gamma) could be increased more than 10-fold by 0.1 mM
zinc. This could not be observed during stimulation with phytohaemagglutin (PHA). In contrast, zinc levels concentration-dependently down-regulated monocyte activation caused by the %%%superantigens%%%, %%%staphylococcal%%%
enterotoxins A and E (SEA, SEE, more than 90% down-regulation by 0.1 mM
zinc), the Mycoplasma arthritidis-derived %%%superantigen%%% (MAS), but not
toxic shock syndrome toxin-1 (TSST-1), while T-cell response remained unaffected. This was not the result of chemical degradation of the %%%superantigens%%% . We assume that zinc concentration regulates
interactions between SEA, SEE and MAS, but not TSST-1 and their major
histocompatibility complex (MHC) class II-binding sites. Our data demonstrate that zinc levels control the secretion of IFN-gamma and monokines after both LPS and %%%superantigen%%% challenge within a
clinically relevant range of concentrations. This reveals new perspectives and indications for zinc supplementation and also indicates potential risks of therapeutic application of zinc.
Record Date Created: 19950622
Record Date Completed: 19950622

11/7/68 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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07862431 93318112 PMID: 8327863

University,-
S-901 85, Umea, Sweden**Sweden E-Mail: anna.eriksoon@climi.umu.se
JOURNAL: Infection and Immunity 71 (1):p211-217 January 2003 2003
MEDIUM: print
ISSN: 0019-9567
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Group A streptococci (GAS) express a %%%superantigen%%%, SpeB,
having cysteine protease activity. SpeB exhibits several properties that might contribute to virulence, the most recently discovered being the ability to cleave immunoglobulin G (IgG) in a manner similar to that of papain. In the present study, we confirmed this latter finding and found that the irreversible inhibition of SpeB protease activity completely abolishes IgG cleavage. SpeB cleavage of IgG was not species restricted since SpeB cleaved both human, rabbit, and mouse IgG. In order to investigate the nature of the SpeB cleavage of IgG, antibodies were immobilized prior to exposure to SpeB, either by unspecific binding of the Fc to GAS surface proteins or by antigen-specific binding. Analysis of the IgG molecules by SDS-PAGE showed that SpeB could cleave antigen-bound antibodies, while the IgG bound to IgG-binding proteins was protected from cleavage. In a phagocytosis assay using whole blood, the M49 GAS strain NZ131 showed a significantly higher survival than its isogenic speB %%%mutant%%%. Furthermore, the addition of extracellular supernatant derived from an overnight culture of native NZ131 increased the survival of its isogenic speB derivative. This indicates that SpeB's ability to cleave off the Fc part of antigen-bound IgG contributes to GAS escape from opsonophagocytosis while not interfering with the formation of a host-like coat by unspecific IgG binding.

2/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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14073912 BIOSIS NO.: 200300067941
Evidence for plasticity and structural mimicry at the immunoglobulin light chain-protein L interface.
AUTHOR: Graille Marc; Harrison Steven; Crump Matthew P; Findlow Stuart C;
Housden Nicholas G; Muller Bruno H; Battail-Poirot Nicole; Sibai Genevieve; Sutton Brian J; Taussig Michael J; Jolivet-Reynaud Colette; Gore Michael G(a); Stura Enrico A
AUTHOR ADDRESS: (a)Department of Biochemistry, Institute of Biomolecular
Sciences, University of Southampton, Bassett Crescent East, Southampton, SO16 7PX, UK**UK E-Mail: M.G.Gore@soton.ac.uk, estura@cea.fr
JOURNAL: Journal of Biological Chemistry 277 (49):p47500-47506 December 6
2002 2002
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The multidomain bacterial surface protein L (PpL) is a virulence factor expressed by only 10% of Peptostreptococcus magnus strains, and its expression is correlated with bacterial vaginosis. The molecular basis for its ability to recognize 60% of mammalian immunoglobulin light chain variable regions (VL) has been described recently by x-ray crystallography, which suggested the presence of two VL binding sites on each protein L domain (Graille, M., Stura, E. A., Housden, N. G., Beckingham, J. A., Bottomley, S. P., Beale, D., Taussig, M. J., Sutton, B. J., Gore, M. G., and Charbonnier, J. (2001) Structure 9, 679-687). Here, we report the crystal structure at 2.1 ANG resolution of a protein L %%%mutant%%% complexed to an Fab' fragment with only 50% of the VL
residues interacting with PpL site 1 conserved. Comparison of the site 1 interface from both structures shows how protein L is able to accommodate
these sequence differences and therefore bind to a large repertoire of Ig. The x-ray structure and NMR results confirm the existence of two VL binding sites on a single protein L domain. These sites exhibit a remarkable structural mimicry of growth factors binding to their receptors. This could explain the protein L %%%superantigenic%%% activity
on human B lymphocytes.
? ds

Set Items Description
S1 1773 SUPERANTIGEN? AND (MUTANT? OR VARIANT? OR NON(W)TOXIC)
S2 850 RD S1 (unique items)
? s s2 and enterotoxin?
850 S2
60438 ENTEROTOXIN?
S3 357 S2 AND ENTEROTOXIN?
? t s3/7/1-5
>>>Format 7 is not valid in file 143

3/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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14207879 BIOSIS NO.: 200300201908
Zinc binding and dimerization of Streptococcus pyogenes pyrogenic exotoxin C are not essential for T-cell stimulation.
AUTHOR: Swietnicki Wieslaw(a); Barnie Anne M; Dyas Beverly K; Ulrich Robert
G
AUTHOR ADDRESS: (a)United States Army Medical Research Institute of Infectious Diseases, Frederick, MD, 21702, USA**USA E-Mail: wes.swietnicki@amedd.army.mil, ulrich@ncifcrf.gov
JOURNAL: Journal of Biological Chemistry 278 (11):p9885-9895 March 14 2003
2003
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Streptococcal pyrogenic %%%enterotoxin%%% C (Spe-C) is a %%%superantigen%%% virulence factor produced by Streptococcus pyogenes
that activates T-cells polyclonally. The biologically active form of Spe-C is thought to be a homodimer containing an essential zinc coordination site on each subunit, consisting of the residues His167, His201, and Asp203. Crystallographic data suggested that receptor specificity is dependent on contacts between the zinc coordination site of Spe-C and the beta-chain of the major histocompatibility complex type II (MHCII) molecule. Our results indicate that only a minor fraction of dimer is present at T-cell stimulatory concentrations of Spe-C following mutation of the unpaired side chain of cysteine at residue 27 to serine. Mutations of amino acid residues His167, His201, or Asp203 had only minor effects on protein stability but resulted in greatly diminished MHCII binding, as measured by surface plasmon resonance with isolated receptor/ligand pairs and flow cytometry with MHCII-expressing cells. However, with the exception of the %%%mutants%%% D203A and D203N, mutation of the zinc-binding site of Spe-C did not significantly impact T-cell activation. The mutation Y76A, located in a polar pocket conserved among most %%%superantigens%%%, resulted in significant loss of T-cell stimulation, although no effect was observed on the overall binding to human MHCII molecules, perhaps because of the masking of this lower affinity interaction by the dominant zinc-dependent binding. To a lesser extent, mutations of side chains found in a second conserved MHCII alpha-chain-binding site consisting of a hydrophobic surface loop decreased T-cell stimulation. Our results demonstrate that dimerization and zinc coordination are not essential for biological activity of Spe-C and suggest the contribution of an alternative MHCII binding mode to T-cell activation.

3/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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14022264 BIOSIS NO.: 200300016293
2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) induces Fas-dependent

tumor-assocd., C-antigen; detection and treatment of cancer with monoclonal antibodies and antibody constructs to
Alkaloids,biological studies...
vinca, conjugates; with antibody constructs targeting C-antigen of tumors
CAS REGISTRY NUMBERS:
200298-81-3 amino acid sequence; treatment and detection of cancer
330989-45-2 330989-46-3 330989-47-4 330989-48-5 330989-49-6 binding specificity for antibodies to C-antigen
50-18-0D 50-44-2D 50-76-0D 51-21-8D 53-19-0D 54-91-1D 55-86-7D 59-05-2D 66-75-1D 143-67-9D 147-94-4D 148-82-3D 154-42-7D 1404-00-8D 1406-72-0D 2068-78-2D 4342-03-4D 9013-93-8D 9041-93-4D 13010-47-4D 15663-27-1D 18883-66-4D 20830-81-3D 23214-92-8D 25316-40-9D 33069-62-4D 33419-42-0D 41575-94-4D 53910-25-1D 59917-39-4D conjugates, with antibody constructs targeting C-antigen of tumors
58-85-5 for immobilization of antibody constructs targeting C-antigen of tumors
200298-80-2 nucleotide sequence; treatment and detection of cancer
15750-15-9D single-chain antibody conjugates, biological studies, for imaging of tumors expressing C-antigen
83869-56-1D single-chain antibody fusion products, to C-antigen of tumors
200298-76-6 200298-78-8 200298-82-4 330490-79-4 331290-27-8 331290-28-9 331290-29-0 331290-30-3 331290-31-4 331290-32-5 331290-34-7 331290-36-9 unclaimed nucleotide sequence; monoclonal antibody to C-antigen, Prophylaxis and detection of cancer
331290-25-6 331290-26-7 331290-33-6 331290-35-8 unclaimed protein sequence; monoclonal antibody to C-antigen, Prophylaxis and detection of cancer
200066-75-7 Unclaimed; monoclonal antibody to C-antigen, Prophylaxis and detection of cancer

8/7/77 (Item 7 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

130342847 CA: 130(25)342847v JOURNAL
Preparation and identification of conjugate of monoclonal antibody against hepatocellular carcinoma HAb18F(ab')2 fragment and staphylococcal enterotoxin A
AUTHOR(S): Yang, Lianjun; Sui, Yanfang; Chen, Zhinan; Liu, Chenggang; Wang, Wenxue
LOCATION: Department of Pathology, Faculty of Preclinical Medicine, Fourth Military Medical University, Xi'an, Peop. Rep. China, 710033
JOURNAL: Disi Junyi Daxue Xuebao DATE: 1998 VOLUME: 19 NUMBER: 6
PAGES: 618-620 CODEN: DJDXEG ISSN: 1000-2790 LANGUAGE: Chinese
PUBLISHER: Disi Junyi Daxue Xuebao Bianjibu
SECTION:
CA263005 Pharmaceuticals
CA215XXX Immunochemistry
IDENTIFIERS: superantigen staphylococcal enterotoxin monoclonal antibody antitumor, hepatocellular carcinoma immunotoxin
DESCRIPTORS:
Enterotoxins...
A; prepn. and identification of conjugate of monoclonal antibody against hepatocellular carcinoma HAb18F(ab')2 fragment and staphylococcal enterotoxin A
Monoclonal antibodies...
hepatocellular carcinoma-recognizing; prepn. and identification of conjugate of monoclonal antibody against hepatocellular carcinoma HAb18F(ab')2 fragment and staphylococcal enterotoxin A
Antitumor agents... Drug targeting... Fusion proteins(chimeric proteins)...

injections, i.v.; bacterial superantigen-antibody conjugates for treating human proliferative diseases or cancers
Histocompatibility antigens...
MHC (major histocompatibility complex), class II; bacterial superantigen-antibody conjugates for treating human proliferative diseases or cancers
Mammary gland... Prostate gland...
neoplasm; bacterial superantigen-antibody conjugates for treating human proliferative diseases or cancers
Disease,animal...
proliferative; bacterial superantigen-antibody conjugates for treating human proliferative diseases or cancers
Mutagenesis...
site-directed, substitution; bacterial superantigen-antibody conjugates for treating human proliferative diseases or cancers
Mutagenesis...
site-directed; bacterial superantigen-antibody conjugates for treating human proliferative diseases or cancers
Antigens...
superantigens; bacterial superantigen-antibody conjugates for treating human proliferative diseases or cancers
Antigens...
surface, tumor; bacterial superantigen-antibody conjugates for treating human proliferative diseases or cancers
Toxins...
toxic shock syndrome 1; bacterial superantigen-antibody conjugates for treating human proliferative diseases or cancers
Antigens...
tumor-assocd.; bacterial superantigen-antibody conjugates for treating human proliferative diseases or cancers
CAS REGISTRY NUMBERS:
483390-43-8P 483391-20-4P 483391-21-5P 483391-22-6P
483391-23-7P amino
acid sequence; bacterial superantigen-antibody conjugates for treating human proliferative diseases or cancers
483392-69-4 483392-70-7 unclaimed protein sequence; bacterial superantigen-antibody conjugates for treating human proliferative diseases or cancers
? ds

Set Items Description
S1 1773 SUPERANTIGEN? AND (MUTANT? OR VARIANT? OR NON(W)TOXIC)
S2 850 RD S1 (unique items)
S3 357 S2 AND ENTEROTOXIN?
S4 346 S3 AND STAPHYLOCOCC?
S5 9 S4 AND ENTEROTOXIN(W)E
S6 73 S4 AND ENTEROTOXIN(W)A
S7 68 S6 NOT S5
S8 399 ENTEROTOXIN(W)E AND STAPHYLOCOCC?
S9 188 RD S8 (unique items)
S10 83 S9 AND SUPERANTIGEN?
S11 74 S10 NOT S5
S12 11 S8 AND CONJUG? AND (ANTIBOD? OR IMMUNOGLOB? OR MONOCLONAL)
S13 6 RD S12 (unique items)
? logoff y
30apr03 16:18:54 User226352 Session D689.3
$11.33 2.024 DialUnits File5
$136.50 78 Type(s) in Format 7
$136.50 78 Types
$147.83 Estimated cost File5
$1.58 0.268 DialUnits File6
$1.58 Estimated cost File6
$95.39 5.156 DialUnits File34
$197.95 37 Type(s) in Format 7
$197.95 37 Types
$293.34 Estimated cost File34
$0.62 0.090 DialUnits File40
$0.62 Estimated cost File40
$2.12 0.471 DialUnits File50
$2.12 Estimated cost File50
$0.63 0.167 DialUnits File65
$0.63 Estimated cost File65
$7.79 1.031 DialUnits File71
$6.72 4 Type(s) in Format 7
$6.72 4 Types
$14.51 Estimated cost File71
$17.63 1.959 DialUnits File73
$27.50 11 Type(s) in Format 7
$27.50 11 Types
$45.13 Estimated cost File73
$1.16 0.332 DialUnits File94
$1.35 1 Type(s) in Format 7
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$2.51 Estimated cost File94
$1.75 0.729 DialUnits File98
$6.70 2 Type(s) in Format 7
$6.70 2 Types
$8.45 Estimated cost File98
$2.33 0.457 DialUnits File103
$2.33 Estimated cost File103
$0.24 0.102 DialUnits File143
$0.24 Estimated cost File143
$4.06 1.160 DialUnits File144
$3.30 2 Type(s) in Format 7
$3.30 2 Types
$7.36 Estimated cost File144
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$4.83 23 Type(s) in Format 7
$4.83 23 Types
$15.82 Estimated cost File155
$3.25 0.608 DialUnits File156
$2.85 3 Type(s) in Format 7
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$6.10 Estimated cost File156
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$0.89 Estimated cost File162
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$1.02 Estimated cost File172
$0.85 0.109 DialUnits File305
$0.85 Estimated cost File305
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$0.29 Estimated cost File369
$0.37 0.105 DialUnits File370
$1.50 1 Type(s) in Format 7
$1.50 1 Types
$1.87 Estimated cost File370
$13.73 1.094 DialUnits File399
$13.75 5 Type(s) in Format 7
$13.75 5 Types
$27.48 Estimated cost File399
$4.70 0.254 DialUnits File434
$4.70 Estimated cost File434
OneSearch, 22 files, 19.941 DialUnits FileOS
$4.42 TELNET
$590.09 Estimated cost this search
$590.13 Estimated total session cost 20.165 DialUnits
Logoff: level 02.13.02 D 16:18:55

5/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12591597 BIOSIS NO.: 200000345099
The spectral and thermodynamic properties of %%%staphylococcal%%% %%%enterotoxin%%% A, E, and %%%variants%%% suggest that structural modifications are important to control their function.
AUTHOR: Cavallin Anders; Arozenius Helena; Kristensson Karin; Antonsson Per
; Otzen Daniel E; Bjork Per; Forsberg Goran(a)
AUTHOR ADDRESS: (a)Active Biotech Research AB, 22007, Lund**Sweden
JOURNAL: Journal of Biological Chemistry 275 (3):p1665-1672 January 21, 2000
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The %%%superantigens%%% %%%staphylococcal%%% %%%enterotoxin%%% A and E (SEA and SEE) can activate a large number of T-cells. SEA and SEE have approximately 80% sequence identity but show some differences in their biological function. Here, the two %%%superantigens%%% and analogues were characterized biophysically. SEE was shown to have a substantially higher thermal stability than SEA. Both SEA and SEE were thermally stabilized by 0.1 mM Zn2+ compared with Zn2+-reduced conditions achieved using 1 mM EDTA or specific replacements that affect Zn2+ coordination. The higher stability of SEE was only partly caused by the T-cell receptor (TCR) binding regions, whereas regions in the vicinity of the major histocompatibility complex class II binding sites affected the stability to a greater extent. SEE exhibited a biphasic denaturation between pH 5.0-6.5, influenced by residues in the TCR binding regions. Interestingly, enzyme-linked immunosorbent assay, isoelectric focusing, and circular dichroism analysis indicated that conformational changes had occurred in the SEA/E chimerical constructs relative to SEA and SEE. Thus, it is proposed that the Zn2+ binding site is very important for the stability and potency of SEA and SEE, whereas residues in the TCR binding site have a substantial influence on the molecular conformation to control specificity and function.

5/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12119683 BIOSIS NO.: 199900414532
Analysis of functional regions of YPM, a %%%superantigen%%% derived from gram-negative bacteria.
AUTHOR: Ito Yasuhiko; Seprenyi Gyorgy; Abe Jun; Kohsaka Takao(a)
AUTHOR ADDRESS: (a)National Children's Medical Research Center, 3-35-31 Taishido, Setagaya, Tokyo, 154-8509**Japan
JOURNAL: European Journal of Biochemistry 263 (2):p326-337 July, 1999
ISSN: 0014-2956
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The bacterial %%%superantigens%%%, %%%staphylococcal%%% %%%enterotoxins%%% and streptococcal pyrogenic exotoxins, are grouped in a family by the conservation of amino acid sequence and polypeptide folding patterns. In the case of Yersinia pseudotuberculosis-derived mitogen (YPM), however, there is no noticeable homology with this family, although many of the in vitro functional features conform to the criteria for a %%%superantigen%%%. To study the mode of action of YPM at the molecular level, we first generated a number of YPM point %%%mutants%%% with reduced T-cell proliferative activity using random mutagenesis and localized the amino acid positions involved in either major histocompatibility complex class II or T-cell receptor Vbeta-interaction. Plotting the elucidated positions on the hydrophilicity profile suggested that they reside mostly on the outer portion of the molecule. We also report that the two cysteines positioned almost at opposing ends of the YPM molecule are connected by an S-S bond the destruction of which causes fatal damage. Finally, we obtained evidence that YPM partially competes with %%%staphylococcal%%% %%%enterotoxin%%% %%%E%%% for human leukocyte antigen-DR binding. This raises the question of whether these different types of %%%superantigens%%% have acquired the same function by genetic convergence or originated from a common ancestral gene.

5/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10998716 BIOSIS NO.: 199799619861
Lck-independent triggering of T-cell antigen receptor signal transduction by %%%staphylococcal%%% %%%enterotoxins%%%.
AUTHOR: Yamasaki Sho; Tachibana Makoto; Shinohara Nobukata; Iwashima Makio (a)
AUTHOR ADDRESS: (a)Mitsubishi Kasei Inst. Life Sci., 11 Minamiooya, Machida, Tokyo 194**Japan
JOURNAL: Journal of Biological Chemistry 272 (23):p14787-14791 1997
ISSN: 0021-9258
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%Superantigens%%% (SAgs) activate T-cells in a manner specific to the V-beta region of the T-cell antigen receptor. Stimulations by SAgs provoke drastic T-cell activation that leads to programmed cell death or the anergic state of responding cells. To characterize the signal transduction pathway initiated by SAgs, %%%mutant%%% lines derived from the human leukemic T-cell line Jurkat were tested for their reactivities against prototypic SAgs, %%%staphylococcal%%% %%%enterotoxins%%%. The J.CaM1.6 cell line, which lacks Lck expression and lost reactivity against T-cell antigen receptor-mediated stimulation, was activated by %%%staphylococcal%%% %%%enterotoxins%%% in a manner indistinguishable from the Jurkat cell line. In contrast, the J.45.01 cell line, which lacks expression of functional CD45, showed severely impaired reactivity. The role of Lck appears to be replaced by another Src family protein-tyrosine kinase, Fyn. In J.CaM1.6 cells, Fyn was rapidly phosphorylated and activated after %%%staphylococcal%%% %%%enterotoxin%%% treatment. The kinase-inactive %%%mutant%%% of Fyn significantly suppressed the reactivity against %%%staphylococcal%%% %%%enterotoxin%%% %%%E%%% in J.CaM1.6 cells, and the expression of the active form of Fyn reconstituted reactivity against %%%staphylococcal%%% %%%enterotoxin%%% %%%E%%% in J.45.01 cells. These results demonstrate that SAgs activate T-cells in an Lck-independent pathway and that Fyn plays a critical role in the process.

5/7/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10789039 BIOSIS NO.: 199799410184
V-alpha domain modulates the multiple topologies of mouse T cell receptor V-beta-20/staphyloccal %%%enterotoxins%%% A and E complexes.
AUTHOR: Bravo De Alba Yolanda(a); Marche Patrice N; Cazenave Pierre-Andrew; Cloutier Isabelle; Sekaly Rafick-Pierre; Thibodeau Jacques
AUTHOR ADDRESS: (a)Unite Biol. Mol. Gene, Inst. Pasteur, 25 rue Dr. Roux,

F-75724 Paris Cedex 15**France
JOURNAL: European Journal of Immunology 27 (1):p92-99 1997
ISSN: 0014-2980
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The %%%superantigens%%% %%%staphylococcal%%% %%%enterotoxin%%% A and E (SEA and SEE) both contact major histocompatibility complex (MHC) class II molecules on two sites located on the alpha and beta chains. We have investigated the role of the T cell receptor (TCR) a chain in the modulation of the various topologies of TCR/SEA (or SEE)/class II complexes. For this purpose, we have used three mouse V-beta-20 T cell lines expressing different V-alpha domains and two T cell hybridomas expressing mouse V-beta-1 or V-beta-11 segments. The response of these T cells to SEA and SEE was studied in the context of presentation by wild-type human MHC class II molecules; or by %%%mutants%%% on MHC, in each of the two %%%superantigen%%% binding sites (position alpha-39K and beta-81H) to which the %%%superantigens%%% can still bind but with an altered conformation. Although V-beta-20 T cell lines are efficiently stimulated using SEA and SEE presented by wild-type HLA-DR1 molecules, our results show that the nature of the TCR V-alpha domain can affect differently the recognition of the toxins bound to %%%mutant%%% class II molecules. This suggests that various functional topologies exist for both SEA and SEE/class II complexes and that the T cell response to each of these complexes can be modulated by the V-alpha domain of the TCR. Interestingly, the recognition of SEA and SEE is achieved in different fashions by a given V-beta-20 T cell line.

5/7/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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08819669 BIOSIS NO.: 199395109020
Function of dipeptidyl peptidase IV (CD26, Tp103) in transfected human T cells.
AUTHOR: Hegen Martin; Camerini David; Fleischer Bernhard(a)
AUTHOR ADDRESS: (a)First Dep. Med., Univ. Mainz, Langenbeckstrasse 1, D-6500 Mainz**Germany
JOURNAL: Cellular Immunology 146 (2):p249-260 1993
ISSN: 0008-8749
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: CD26 (Tp103) is a proteolytic enzyme (dipeptidyl peptidase IV) expressed on the T cell surface that defines an alternative activation signal for human T lymphocytes. It is absent from or present in only low amounts on resting T cells but it is expressed strongly after activation. Crosslinking of CD26/Tp103 via the monoclonal antibody CB.1 triggers functional activities in preactivated T cells. To study the molecular requirements for T cell activation via CD26 we transfected a cDNA encoding CD26 into several CD26-negative cells. In Jurkat T cell leukemia cells that normally do not express the CD26 antigen, the transfected CD26 molecule is functional because the monoclonal antibody CB.1 induces an increase of cytosolic Ca-2+ concentration and IL-2 production. For this stimulatory effect a crosslinking of the monoclonal antibody CB.1 is necessary. After modulation of the TCR/CD3 complex the transfected Jurkat cells were insensitive to triggering via CD26. Moreover, a CD26-transfected TCR-negative %%%variant%%% Jurkat cells did not respond to CD26 triggering despite high levels of expression of the molecule on their surface. These data demonstrate that the function of CD26/Tp103 is dependent on the expression of the T cell receptor complex. In search of a physiological function of CD26 we found a costimulatory effect of mAb CB.1 in combination with the nonstimulatory anti-CD3 antibody BMA030 and an additive effect in the response to the %%%superantigen%%% %%%staphylococcal%%% %%%enterotoxin%%% %%%E%%%. Transfected Jurkat cells, however, did not show a reproducibly enhanced responsiveness to the %%%superantigen%%% compared to that of untransfected cells.

5/7/8 (Item 1 from file: 98)
DIALOG(R)File 98:General Sci Abs/Full-Text
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04517791 H.W. WILSON RECORD NUMBER: BGSA01017791 (THIS IS THE FULLTEXT)
Toxic shock syndrome and bacterial %%%superantigens%%%: an update.
McCormick, John K
Yarwood, Jeremy M; Schlievert, Patrick M
Annual Review of Microbiology v. 55 (2001) p. 77-104
LANGUAGE: English
COUNTRY OF PUBLICATION: United States
WORD COUNT: 13798

ABSTRACT: Toxic shock syndrome (TSS) is an acute onset illness characterized by fever, rash formation, and hypotension that can lead to multiple organ failure and lethal shock, as well as desquamation in patients that recover. The disease is caused by bacterial %%%superantigens%%% (SAGs) secreted from %%%Staphylococcus%%% aureus and group A streptococci. SAGs bypass normal antigen presentation by binding to class II major histocompatibility complex molecules on antigen-presenting cells and to specific variable regions on the b-chain of the T-cell antigen receptor. Through this interaction, SAGs activate T cells at orders of magnitude above antigen-specific activation, resulting in massive cytokine release that is believed to be responsible for the most severe features of TSS. This review focuses on clinical and epidemiological aspects of TSS, as well as important developments in the genetics, biochemistry, immunology, and structural biology of SAGs. From the evolutionary relationships between these important toxins, we propose that there are five distinct groups of SAGs. Reprinted by permission of the publisher.

TEXT:
Key Words %%%Staphylococcus%%% aureus, Streptococcus pyogenes, hypotension, T cell stimulation

INTRODUCTION
Toxic shock syndrome (TSS), which has been sporadically reported as %%%staphylococcal%%% scarlet fever since 1927 (154), was first formally described by Todd and colleagues in 1978 in a landmark paper that recognized the disease as a major systemic illness associated with noninvasive %%%Staphylococcus%%% aureus infection in children (164). Major interest in the disease was sparked during the early 1980s when a significant number of %%%staphylococcal%%% TSS cases occurred in otherwise healthy young women using high-absorbency tampons (32, 146). Although TSS has traditionally been associated with S. aureus, it is clear that the group A streptococci (GAS; Streptococcus pyogenes) also cause a similar disease.

The fundamental hypothesis for the development of TSS is that infection with S. aureus or GAS results in the production of toxin, which in turn leads to illness. %%%Staphylococcal%%% TSS patients do not normally have detectable bacteremia, yet clinical features of the disease are systemic, suggesting that TSS results from an intoxication with bacterial products. In 1981 two research groups independently characterized a secreted protein from S. aureus that was highly associated with menstrual-associated TSS (11, 144). This toxin, named toxic shock syndrome toxin-1 (TSST-1) (12), is responsible for nearly all cases of menstrual-associated TSS. This association is likely due to its apparent unique ability among these toxins to cross mucosal barriers (142). Nonmenstrual-associated %%%staphylococcal%%% TSS is normally associated with TSST-1, %%%staphylococcal%%% %%%enterotoxin%%% (SE) serotype B (SEB), or SEC (15, 137).

Although %%%staphylococcal%%% TSS often occurs with localized infection, streptococcal TSS generally occurs concurrent with an invasive episode of streptococcal disease that may include bacteremia, cellulitis, necrotizing fasciitis, or myonecrosis. The erythrogenic toxins from GAS

non-menstrual TSS. Lancet 1:1149-50
138. Schlievert PM. 1997. Incidence studies of toxic shock syndrome. Int. Congr. Symp. Ser., Eur. Conf. Toxic Shock Syndrome, p. 34-36. London: R. Soc. Med. Press
139. Schlievert PM, Assimacopoulos AP, Cleary PP. 1996. Severe invasive group A streptococcal disease: clinical description and mechanisms of pathogenesis. J. Lab. Clin. Med. 127:13-22
140. Schlievert PM, Blomster DA. 1983. Production of %%%staphylococcal%%% pyrogenic exotoxin type C: influence of physical and
chemical factors. J. Infect. Dis. 147:236-42
141. Schlievert PM, Gray ED. 1989. Group A streptococcal pyrogenic exotoxin (scarlet fever toxin) type A and blastogen A are the same protein. Infect. Immun. 57:1865-67
142. Schlievert PM, Jablonski LM, Roggiani M, Sadler I, Callantine S, et al. 2000. Pyrogenic toxin %%%superantigen%%% site specificity in toxic shock syndrome and food poisoning in animals. Infect. Immun. 68:3630-34
143. Schlievert PM, Kotb MY, Stevens DL. 2000. Streptococcal %%%superantigens%%%: streptococcal toxic shock syndrome. See Ref. 30a, pp.
25-39
144. Schlievert PM, Shands KN, Dan BB, Schmid GP, Nishimura RD. 1981. Identification and characterization of an exotoxin from %%%Staphylococcus%%% aureus associated with toxic-shock syndrome. J. Infect. Dis. 143:509-16
145. Seth A, Stern LJ, Ottenhoff TH, Engel I, Owen MJ, et al. 1994. Binary and ternary complexes between T-cell receptor, class II MHC and %%%superantigen%%% in vitro. Nature 369:324-27
146. Shands KN, Schmid GP, Dan BB, Blum D, Guidotti RJ, et al. 1980. Toxic-shock syndrome in menstruating women: association with tampon use and
%%%Staphylococcus%%% aureus and clinical features in 52 cases. N. Engl. J.
Med. 303:1436-42
147. Shimizu Y. 2000. Streptococcal toxic shock-like syndrome. Intern. Med. 39:195-6
148. Stanley J, Desai M, Xerry J, Tanna A, Efstratiou A, et al. 1996. High-resolution genotyping elucidates the epidemiology of group A streptococcus outbreaks. J. Infect. Dis. 174:500-6
149. Stegmayr B, Bjorck S, Holm S, Nisell J, Rydvall A, et al. 1992. Septic shock induced by group A streptococcal infection: clinical and therapeutic aspects. Scand. J. Infect. Dis. 24:589-97
150. Stevens DL. 1995. Could nonsteroidal antiinflammatory drugs (NSAIDs) enhance the progression of bacterial infections to toxic shock syndrome? Clin. Infect. Dis. 21:977-80
151. Stevens DL. 1995. Streptococcal toxic-shock syndrome: spectrum of disease, pathogenesis, and new concepts in treatment. Emerg. Infect. Dis. 1:69-78
152. Stevens DL. 2000. Streptococcal toxic shock syndrome associated with necrotizing fasciitis. Annu. Rev. Med. 51:271-88
153. Stevens DL, Tanner MH, Winship J, Swarts R, Ries KM, et al. 1989. Severe group A streptococcal infections associated with a toxic shock-like syndrome and scarlet fever toxin A. N. Engl. J. Med. 321:1-7
154. Stevens FA. 1927. The occurrence of %%%Staphylococcus%%% aureus
infection with a scarlatiniform rash. JAMA 88:1957-58
155. Stolz SJ, Davis JP, Vergeront JM, Crass BA, Chesney PJ, et al. 1985. Development of serum antibody to toxic shock toxin among individuals with toxic shock syndrome in Wisconsin. J. Infect. Dis. 151:883-89
156. Su YC, Wong AC. 1995. Identification and purification of a new %%%staphylococcal%%% %%%enterotoxin%%%, H. Appl. Environ. Microbiol. 61:1438-43
157. Sundberg E, Jardetzky TS. 1999. Structural basis for HLA-DQ binding by the streptococcal %%%superantigen%%% SSA. Nat. Struct. Biol. 6:123-29
158. Sundstrom M, Abrahmsen L, Antonsson P, Mehindate K, Mourad W, et
al. 1996. The crystal structure of %%%staphylococcal%%% %%%enterotoxin%%%
type D reveals Zn2+-mediated homodimerization. EMBO J. 15:6832-40
159. Sundstrom M, Hallen D, Svensson A, Schad E, Dohlsten M, et al. 1996. The co-crystal structure of %%%staphylococcal%%% %%%enterotoxin%%%
type A with Zn2+ at 2.7 A resolution. Implications for major histocompatibility complex class II binding. J. Biol. Chem. 271:32212-16
160. Swaminathan S, Furey W, Pletcher J, Sax M. 1992. Crystal structure of %%%staphylococcal%%% %%%enterotoxin%%% B, a %%%superantigen%%%
. Nature 359:801-6
161. Talkington DF, Schwartz B, Black CM, Todd JK, Elliott J, et al. 1993. Association of phenotypic and genotypic characteristics of invasive Streptococcus pyogenes isolates with clinical components of streptococcal toxic shock syndrome. Infect. Immun. 61:3369-74
162. Deleted in press
163. Thompson JD, Higgins DG, Gibson TJ. 1994. CLUSTAL W: improving the sensitivity of progressive multiple sequence alignment through sequence weighting, position-specific gap penalties and weight matrix choice. Nucleic Acids Res. 22:4673-80
164. Todd JK, Kapral FA, Fishaut M, Welch TR. 1978. Toxic shock syndrome associated with phage group I %%%staphylococci%%%. Lancet 2:1116-18
165. Todd JK, Todd BH, Franco-Buff A, Smith CM, Lawellin DW. 1987. Influence of focal growth conditions on the pathogenesis of toxic shock syndrome. J. Infect. Dis. 155:673-81
166. Ulrich RG. 2000. Evolving %%%superantigens%%% of %%%Staphylococcus%%% aureus. FEMS Immunol. Med. Microbiol. 27:1-7
167. Vergeront JM, Stolz SJ, Crass BA, Nelson DB, Davis JP, et al. 1983. Prevalence of serum antibody to %%%staphylococcal%%% %%%enterotoxin%%% F among Wisconsin residents: implications for toxic-shock
syndrome. J. Infect. Dis. 148:692-98
168. Wagner G, Bohr L, Wagner P, Petersen LN. 1984. Tampon-induced changes in vaginal oxygen and carbon dioxide tensions. Am. J. Obstet. Gynecol. 148:147-50
169. Watanabe-Ohnishi R, Low DE, McGeer A, Stevens DL, Schlievert PM,
et al. 1995. Selective depletion of V beta-bearing T cells in patients with severe invasive group A streptococcal infections and streptococcal toxic shock syndrome. Ontario Streptococcal Study Project. J. Infect. Dis. 171:74-84
170. Watson DW. 1959. Host-parasite factors in group A streptococcal infections: pyrogenic and other effects on immunologic distinct exotoxins relating to scarlet fever toxins. J. Exp. Med. 111:255-83
171. Weeks CR, Ferretti JJ. 1986. Nucleotide sequence of the type A streptococcal exotoxin (erythrogenic toxin) gene from Streptococcus pyogenes bacteriophage T12. Infect. Immun. 52:144-50
172. Wong AC, Bergdoll MS. 1990. Effect of environmental conditions on production of toxic shock syndrome toxin 1 by %%%Staphylococcus%%% aureus.
Infect. Immun. 58:1026-29
172a. Working Group on Severe Streptococcal Infections. 1993. Defining the group A streptococcal toxic shock syndrome. Rationale and consensus definition. JAMA 269:390-91
173. Yarwood JM, Leung DY, Schlievert PM. 2000. Evidence for the involvement of bacterial %%%superantigens%%% in psoriasis, atopic dermatitis, and Kawasaki syndrome. FEMS Microbiol. Lett. 192:1-7
174. Yarwood JM, Schlievert PM. 2000. Oxygen and carbon dioxide regulation of toxic shock syndrome toxin 1 production by %%%Staphylococcus%%% aureus MN8. J. Clin. Microbiol. 38:1797-803
175. Zabriskie J. 1964. The role of temperate bacteriophage in the production of erythrogenic toxin by group A streptococci. J. Exp. Med. 119:761-80
176. Zerr DM, Alexander ER, Duchin JS, Koutsky LA, Rubens CE. 1999. A case-control study of necrotizing fasciitis during primary varicella. Pediatrics 103:783-90
177. Zhang S, Iandolo JJ, Stewart GC. 1998. The %%%enterotoxin%%% D
plasmid of %%%Staphylococcus%%% aureus encodes a second %%%enterotoxin%%%
determinant (sej). FEMS Microbiol. Lett. 168:227-33

10823278 97174269 PMID: 9022003

V alpha domain modulates the multiple topologies of mouse T cell receptor V beta20/%%%staphylococcal%%% %%%enterotoxins%%% A and E complexes.

Bravo de Alba Y; Marche P N; Cazenave P A; Cloutier I; Sekaly R P; Thibodeau J

Departement d'Immunologie, Institut Pasteur (URA CNRS 1961 and Universite
Pierre et Marie Curie), Paris, France. ybravo@pasteur.fr
European journal of immunology (GERMANY) Jan 1997, 27 (1) p92-9, ISSN 0014-2980 Journal Code: 1273201
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The %%%superantigens%%% %%%staphylococcal%%% %%%enterotoxin%%% A and E
(SEA and SEE) both contact major histocompatibility complex (MHC) class II
molecules on two sites located on the alpha and beta chains. We have investigated the role of the T cell receptor (TCR) alpha chain in the modulation of the various topologies of TCR/SEA (or SEE)/class II complexes. For this purpose, we have used three mouse V beta20 T cell lines expressing different V alpha domains and two T cell hybridomas expressing mouse V beta1 or V beta11 segments. The response of these T cells to SEA and SEE was studied in the context of presentation by wild-type human MHC
class II molecules; or by %%%mutants%%% on MHC, in each of the two
%%%superantigen%%% binding sites (position alpha39K and beta81H) to which
the %%%superantigens%%% can still bind but with an altered conformation.
Although V beta20 T cell lines are efficiently stimulated using SEA and SEE presented by wild-type HLA-DR1 molecules, our results show that the nature
of the TCR V alpha domain can affect differently the recognition of the toxins bound to %%%mutant%%% class II molecules. This suggests that various
functional topologies exist for both SEA and SEE/class II complexes and that the T cell response to each of these complexes can be modulated by the
V alpha domain of the TCR. Interestingly, the recognition of SEA and SEE is achieved in different fashions by a given V beta20 T cell line.
Record Date Created: 19970305
Record Date Completed: 19970305
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Set Items Description
S1 1773 SUPERANTIGEN? AND (MUTANT? OR VARIANT? OR NON(W)TOXIC)
S2 850 RD S1 (unique items)
S3 357 S2 AND ENTEROTOXIN?
S4 346 S3 AND STAPHYLOCOCC?
S5 9 S4 AND ENTEROTOXIN(W)E
? s s4 and enterotoxin(w)A
Processing
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Processed 10 of 22 files ...
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346 S4
51162 ENTEROTOXIN
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7/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

14022264 BIOSIS NO.: 200300016293
2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) induces Fas-dependent activation-induced cell death in %%%superantigen%%%-primed T cells.
AUTHOR: Camacho Iris A; Nagarkatti Mitzi; Nagarkatti Prakash S(a)
AUTHOR ADDRESS: (a)Department of Pharmacology and Toxicology, Virginia
Commonwealth University, Medical College of Virginia Campus, PO Box 980613, Richmond, VA, 23298-0613, USA**USA E-Mail: pnagark@hsc.vcu.edu
JOURNAL: Archives of Toxicology 76 (10):p570-580 October 2002 2002
MEDIUM: print
ISSN: 0340-5761
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Immune response against a foreign antigen is characterized by a
growth phase, in which antigen-specific T cells clonally expand, followed by a decline phase in which the activated T cells undergo apoptosis, a process termed activation-induced cell death (AICD). In the current study, we have investigated the phase at which 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) acts to downregulate the antigen-specific T cell response. To this end, C57BL/6 +/+ mice were injected with %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%% (SEA) into
the footpads (10 mug/footpad), and simultaneously treated with TCDD (10 or 50 mug/kg intraperitoneally). At various time points, the draining lymph node (LN) cells were analyzed for SEA-activated T cells. The data demonstrated that in C57BL/6 +/+ mice, TCDD treatment did not alter the growth phase but facilitated the decline phase of SEA-reactive T cells. TCDD caused a significant decrease in the percentage and absolute numbers
of CD4+ and CD8+ SEA-responsive T cells expressing Vbeta3+ and Vbeta11+ but did not affect SEA-nonresponsive Vbeta8+ T cells. Upon in vitro culture, TCDD-exposed SEA-immunized LN cells exhibited increased levels of apoptosis when compared with the vehicle controls. When Fas-deficient (C57BL/6 lpr/lpr) or Fas ligand defective (C57BL/6 gld/gld) mice were treated with TCDD, they failed to exhibit a decrease in percentage and cellularity of SEA-reactive T cells, thereby suggesting a role of Fas-Fas ligand interactions in the TCDD-induced downregulation of SEA-reactive T cell response. The resistance to TCDD-induced decrease in T cell responsiveness to SEA seen in Fas- and FasL-%%%mutant%%% mice was neither
due to decreased aryl hydrocarbon receptor (AhR) expression nor to altered T cell responsiveness to SEA. The current study demonstrates that TCDD does not prevent T cell activation, but prematurely induces Fas-based AICD, which may contribute to the deletion of antigen-primed T cells.

7/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13688180 BIOSIS NO.: 200200317001
T-cell immunotherapy for human MK-1-expressing tumors using a fusion protein of the %%%superantigen%%% SEA and anti-MK-1 scFv antibody.
AUTHOR: Ueno Aruto; Arakawa Fumiko; Abe Hironori; Matsumoto Hisanobu; Kudo
Toshio; Asano Ryutaro; Tsumoto Kohei; Kumagai Izumi; Kuroki Motomu; Kuroki Masahide(a)
AUTHOR ADDRESS: (a)Department of Biochemistry, Fukuoka University School of
Medicine, 7-45-1 Nanakuma, Jonan-ku, Fukuoka, 814-0180**Japan E-Mail: kurokima@fukuoka-u.ac.jp
JOURNAL: Anticancer Research 22 (2A):p769-776 March-April, 2002
MEDIUM: print
ISSN: 0250-7005
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background: The bacterial %%%superantigen%%%

%%%staphylococcal%%%
%%%enterotoxin%%% %%%A%%% (SEA) is an extremely potent activator of T
lymphocytes when presented on major histocompatibility complex (MHC) class II molecules. To develop a tumor-specific %%%superantigen%%% for cancer therapy, we constructed a recombinant fusion protein of SEA and the single-chain variable fragment (scFv) of the FU-MK-1 antibody, which recognizes a glycoprotein antigen (termed MK-1 antigen) present on most carcinomas. Materials and Methods: We employed recombinant DNA techniques
to fuse recombinant %%%mutant%%% SEA to an scFv antibody derived from
FU-MK-1 and the resulting fusion protein (SEA/FUscFv) was produced by a bacterial expression system, purified with a metal-affinity column, and characterized for its MK-1-binding specificity and its antitumor activity. Results: The SEA/FUscFv fusion protein retained the reactivity with MK-1-expressing tumor cells, introduced a specific cytotoxicity of lymphokine-activated killer T-cells to the tumor cells, and consequently suppressed the tumor growth in a SCID mouse xenograft model. Conclusion: This genetically engineered SEA/FUscFv fusion protein may serve as a potentially useful immunotherapeutic reagent for human MK-1-expressing tumors.

7/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13578248 BIOSIS NO.: 200200207069
Structural basis for abrogated binding between %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%% %%%superantigen%%% vaccine and MHC-IIalpha.
AUTHOR: Krupka Heike I; Segelke Brent W; Ulrich Robert G; Ringhofer Sabine;
Knapp Mark; Rupp Bernhard(a)
AUTHOR ADDRESS: (a)Macromolecular Crystallography and Structural Genomics,
Lawrence Livermore National Laboratory, LLNL-BBRP, University of California, L-448, Livermore, CA, 94551**USA E-Mail: br@llnl.gov
JOURNAL: Protein Science 11 (3):p642-651 March, 2002
MEDIUM: print
ISSN: 0961-8368
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%Staphylococcal%%% %%%enterotoxins%%% (SEs) are %%%superantigenic%%% protein toxins responsible for a number of life-threatening diseases. The X-ray structure of a %%%staphylococcal%%%
%%%enterotoxin%%% %%%A%%% (SEA) triple-%%%mutant%%% (L48R, D70R, and
Y92A) vaccine reveals a cascade of structural rearrangements located in three loop regions essential for binding the alpha subunit of major histocompatibility complex class II (MHC-II) molecules. A comparison of hypothetical model complexes between SEA and the SEA triple %%%mutant%%%
with MHC-II HLA-DR1 clearly shows disruption of key ionic and hydrophobic
interactions necessary for forming the complex. Extensive dislocation of the disulfide loop in particular interferes with MHC-IIalpha binding. The triple-%%%mutant%%% structure provides new insights into the loss of %%%superantigenicity%%% and toxicity of an engineered %%%superantigen%%%
and provides a basis for further design of %%%enterotoxin%%% vaccines.

7/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13267145 BIOSIS NO.: 200100474294
Synergistic immunopotentiating effects induced by T-cell and B-cell %%%superantigen%%% in mice.
AUTHOR: Mondal Tapan K; Bhatta D; Ray Prasanta K; Pal Prakriti(a)
AUTHOR ADDRESS: (a)Division of Haematology, Dept. of Pathology and Bacteriology, Institute of Post Graduate Medical Education and Research, 244, A. J. C. Bose Road, Calcutta, 700020**India
JOURNAL: Immunological Investigations 30 (3):p169-180 August, 2001
MEDIUM: print
ISSN: 0882-0139
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: %%%Staphylococcal%%%
%%%Enterotoxin%%%-%%%A%%%(SEA), a 27 kDa
monomeric protein, produced by some strains of %%%Staphylococcus%%% aureus, is a prototype T-cell %%%superantigen%%% which causes proliferation of cytotoxic T-lymphocytes and produces cytokines like TNF-alpha and IFN-gamma. Recently Protein A (PA), a 42 kDa membrane protein of the %%%Staphylococcus%%% aureus Cowan-I strain, has been termed a B-cell super antigen. It has been shown to cause multiple immunological responses. In the present study we examined the effect of these two %%%superantigens%%% used separately as well as combination in a
normal mouse system. It has been shown that combination treatment of PA and SEA is more effective than that of each individual one. FACS analyses of cell cycles showed that a finely turned cellular collaboration occurred in various phases of cell growth and proliferative response compared with controls ($P < 0.01$). It has also been shown that the percentage of various cell types bearing different clusters of differentiation markers, e.g., CD8+, CD34+ increases considerably due to the combined effect of PA and SEA. We also observed that co-administration of both the elicits different soluble mediators like cytokines (TNF-alpha, INF-gamma, IL-1beta). No apoptotic phenomenon was
observed (from the cell cycle analysis) for the dose of PA and SEA, used for the experiments, suggesting that these doses of PA and SEA should be %%%non%%%-%%%toxic%%%.

7/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13026270 BIOSIS NO.: 200100233419
Antagonistic effects of the %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%%
%%%mutant%%%, SEAF47A/D227A, on psoriasis in the SCID-hu xenogeneic
transplantation model.
AUTHOR: Boehncke Wolf-Henning(a); Hardt-Weinelt Katja; Nilsson Helen; Wolter Manfred; Dohlsten Mikael; Ochsendorf Falk-Ruediger; Kaufmann Roland; Antonsson Per
AUTHOR ADDRESS: (a)Department of Dermatology, University of Frankfurt,
Theodor-Stern-Kai 7, D-60590, Frankfurt: Boehncke@em.uni-frankfurt.de**
Germany
JOURNAL: Journal of Investigative Dermatology 116 (4):p596-601 April, 2001
MEDIUM: print
ISSN: 0022-202X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Psoriasis is a T-cell-mediated immune dermatosis probably triggered by bacterial %%%superantigens%%%. This pathomechanism has been
experimentally reproduced in a SCID-hu xenogeneic transplantation model. We analyzed the effects of different bacterial %%%superantigens%%% on the
induction of psoriasis in this model. %%%Staphylococcal%%% %%%enterotoxin%%% B and exfoliative toxin triggered the onset of psoriasis when administered repetitively intracutaneously over a period of 2 wk, whereas %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%%
representing a distinct subfamily of %%%staphylococcal%%%

%%%enterotoxins%%% only mimicked certain aspects of psoriasis. The biologic effects of %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%% were more pronounced when a mutated form, SEAH187A, of this %%%superantigen%%% with reduced affinity to major histocompatibility complex class II was coinjected. Another mutated %%%variant%%%, SEAF47A/D227A, exhibiting no measurable major histocompatibility complex class II affinity blocked the effects triggered by wild-type %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%% when injected in a 10-fold higher dose. Inhibition was specific as induction of psoriasiform epidermal changes by %%%staphylococcal%%% %%%enterotoxin%%% B could not be blocked. As %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%%, in contrast to the other %%%superantigens%%% tested, is capable of inducing epidermal thickening but not the typical appearance of psoriasis, we conclude that bacterial %%%superantigens%%% may differ with regard to their effects on human nonlesional psoriatic skin. %%%Staphylococcal%%%-%%%enterotoxin%%%-%%%A%%%-mediated effects were blocked by a genetically engineered %%%superantigen%%% highlighting the potential therapeutic use of mutated %%%superantigens%%%.

7/7/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13002950 BIOSIS NO.: 200100210099
%%%Superantigen%%% recognition by gammadelta T cells: SEA recognition site for human Vgamma2 T cell receptors.
AUTHOR: Morita Craig T(a); Li Hongmin; Lamphear James G; Rich Robert R; Fraser John D; Mariuzza Roy A; Lee Hoi K
AUTHOR ADDRESS: (a)Division of Rheumatology, Department of Internal Medicine and Interdisciplinary Group in Immunology, University of Iowa College of Medicine, Iowa City, IA, 52242: craig-morita@uiowa.edu**USA
JOURNAL: Immunity 14 (3):p331-344 March, 2001
MEDIUM: print
ISSN: 1074-7613
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Human gammadelta T cells expressing the Vgamma2Vdelta2 antigen receptors recognize nonpeptide prenyl pyrophosphate and alkylamine antigens. We find that they also recognize %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%% %%%superantigens%%% in a manner distinct from the recognition of nonpeptide antigens. Using chimeric and %%%mutant%%% toxins, SEA amino acid residues 20-27 were shown to be required for gammadelta TCR recognition of SEA. Residues at 200-207 that are critical for specific alphabeta TCR recognition of SEA do not affect gammadelta TCR recognition. SEA residues 20-27 are located in an area contiguous with the binding site of V beta chains. This study defines a %%%superantigen%%% recognition site for a gammadelta T cell receptor and demonstrates the differences between Vgamma2Vdelta2+ T cell recognition of %%%superantigens%%% and nonpeptide antigens.

7/7/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11492837 BIOSIS NO.: 199800274169
Antibody-directed %%%superantigen%%%-mediated T-cell killing of myeloid leukaemic cell line cells.
AUTHOR: Gidlof Cecilia; Carlson Barbro; Dohlsten Mikael; Totterman Thomas H (a)
AUTHOR ADDRESS: (a)Dep. Clinical Immunol., University Hosp., S-751 85 Uppsala**Sweden
JOURNAL: European Journal of Haematology 60 (4):p233-239 April, 1998
ISSN: 0902-4441
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Bacterial %%%superantigens%%% (SAgs) bound to MHC class II molecules on target cells are efficient activators of cytotoxic T cells expressing certain T cell receptor (TCR) Vbeta regions. We described earlier that the specificity of the SAg %%%Staphylococcus%%% %%%enterotoxin%%% %%%A%%% (SEA) can be changed by introducing a D227A point mutation in the major MHC class II binding site and by genetically fusing the SEA %%%mutant%%% (SEAm) to protein A (PA). This SEAm-PA fusion protein can then be used to direct cytotoxic T cells to tumour cells coated with monoclonal antibodies (mAbs). In this communication, we tested the PA-SEAm fusion protein together with mAbs against the myeloid cell surface antigens CD13, CD15 and CD33. A SEA-reactive T cell line was used as effector cells against 10 different myeloid leukaemic cell lines. Optimal lysis of antigen positive leukaemic cells was obtained at a PA-SEAm concentration of 1 ng/ml and effector : target cell ratios of 15:1. No correlation between target cell sensitivity and the level of surface antigen expression could be seen. The 6 acute myeloid leukaemia (AML) cell lines tested appeared to be more sensitive than the 4 chronic myeloid leukaemia (CML) cell lines. The sensitivity of the AML cell line HL-60 could be improved further by stimulation with TNFalpha. This was accompanied by increased surface ICAM-1 expression whereas specific target molecule expression (CD13, CD33) was unchanged. This suggests that sensitivity to lysis is related to the leukaemic subtype and ICAM-1 expression but not to the tumour antigen density. Our results show that it is possible to direct cytotoxic T cells to myeloid leukaemia cells by using SAgs linked to mAbs, and encourage the construction and testing of a recombinant direct SAg-mAb fusion protein as a candidate drug for therapy of myeloid leukaemias.

7/7/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11281484 BIOSIS NO.: 199800062816
MHC class II-independent, Vbeta-specific activation of T cells by %%%superantigen%%% %%%mutants%%% fused to anti-tumor antibodies: Implications for use in treatment of human colon carcinoma.
AUTHOR: Newton D(a); Dohlsten M; Lando P; Kalland T; Olsson C; Kotb M(a)
AUTHOR ADDRESS: (a)Univ. Tenn.-Memphis, Memphis, TN**USA
JOURNAL: Human Immunology 55 (SUPPL. 1):p11 1997
CONFERENCE/MEETING: 23rd Annual Meeting of the American Society for Histocompatibility and Immunogenetics Atlanta, Georgia, USA October 14-19, 1997
SPONSOR: The American Society for Histocompatibility and Immunogenetics
ISSN: 0198-8859
RECORD TYPE: Citation
LANGUAGE: English

7/7/9 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11259582 BIOSIS NO.: 199800040914
A mutation of F47 to A in %%%staphylococcus%%% %%%enterotoxin%%% %%%A%%% activates the T-cell receptor Vbeta repertoire in vivo.
AUTHOR: Rosendahl Alexander; Hansson Johan; Antonsson Per; Sekaly

Rafick P;
Kalland Terje; Dohlsten Mikael(a)
AUTHOR ADDRESS: (a)Pharm. Upjohn, Lund Res. Cent., Box 724, S-220 07 Lund**
Sweden
JOURNAL: Infection and Immunity 65 (12):p5118-5124 Dec., 1997
ISSN: 0019-9567
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The bacterial %%%superantigen%%% %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%% (SEA) binds with high affinity to major histocompatibility complex (MHC) class II molecules and subsequently activates T cells bearing particular T-cell receptor (TCR) VP chains. Structural and mutational studies have defined two distinct MHC class II binding sites located in the N-terminal and C-terminal domains of SEA. The N-terminal F47 amino acid is critically involved in a low-affinity interaction to the MHC class II alpha-chain, while the C-terminal residues H187, H225, and D227 coordinate a Zn2+ ion and bind with moderate affinity to the beta-chain. In order to analyze whether the SEA-MHC class II alpha-chain interaction plays a role in dictating the in vivo repertoire of T-cell subsets, we studied distinct VP populations after stimulation with wild-type SEA (SEA(wt)) and SEA with an F47A mutation (SEA(F47A)). Injections of SEA(wt) in C57BL/6 mice induced cytokine release in serum, strong cytotoxic T-lymphocyte activity, expansion of T-cell subsets, and modulated expression of the T-cell activation antigens CD25, CD11a, CD44, CD62L, and CD69. SEA-reactive TCR
Vbeta3+ and Vbeta11+ T cells were activated, while TCR Vbeta8+ T cells remained unaffected. The SEA(F4A) %%%mutant%%% protein induced a weaker
T-cell response and failed to induce substantial interleukin-6 production compared to SEA(,,). Notably, SEA(F47A) failed to activate TCR Vbeta11+ T
cells, whereas in vivo expansion and modulation of T-cell activation markers on TCR Vbeta3+ T cells were similar to those for SEA(wt). A similar response to SEA(F47A) was seen among CD4+ and CD8+ T cells. Activation of TCRVbeta3+ and TCR Vbeta11+ T-cell hybridomas confirmed that SEA(F47A) activates TCR Vbeta3+ but not TCR Vbeta11+ T cells. The data support the view that the SEA-N-terminal MHC class II alpha-chain interaction defines a topology that is required for engagement of certain TCR VP chains in vivo.

7/7/10 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10974360 BIOSIS NO.: 199799595505
Functional analysis of Mycoplasma arthritidis-derived mitogen interactions with class II molecules.
AUTHOR: Bernatchez Chantale; Al-Daccak Reem; Mayer Pierre Etongue; Mehindate Khalil; Rink Lothar; Mecheri Salah; Mourad Walid(a)
AUTHOR ADDRESS: (a)CRRI, CHUL, Room 9800, 2705 Blvd., Laurier, Ste-Foy, PQ
G1V 4G2**Canada
JOURNAL: Infection and Immunity 65 (6):p2000-2005 1997
ISSN: 0019-9567
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The ability of %%%superantigens%%% (SAGs) to trigger various
cellular events via major histocompatibility complex (MHC) class II molecules is largely mediated by their mode of interaction. Having two MHC class II binding sites, %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%% (SEA) is able to dimerize MHC class II molecules on the cell surface and consequently induces cytokine gene expression in human monocytes. In contrast, cross-linking with specific monoclonal antibodies or T-cell receptor is required for %%%staphylococcal%%% %%%enterotoxin%%%
B (SEB) and toxic shock syndrome toxin 1 (TSST-1) to induce similar responses. In the present study, we report how Mycoplasma arthritidis-derived mitogen (MAM) may interact with MHC class II molecules to induce cytokine gene expression in human monocytes. The data presented indicate that MAM-induced cytokine gene expression in human monocytes is Zn-2+ dependent. The MAM-induced response is completely abolished by pretreatment with SEA %%%mutants%%% that have lost their
capacity to bind either the MHC class II alpha or beta chain, with wild-type SEB, or with wild-type TSST-1, suggesting that MAM induces cytokine gene expression most probably by inducing dimerization of class II molecules. In addition, it seems that SEA and MAM interact with the same or overlapping binding sites on the MHC class II beta chain and, on the other hand, that they bind to the alpha chain most probably through the regions that are involved in SEB and TSST-1 binding.

7/7/11 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10938828 BIOSIS NO.: 199799559973
Selection of phage-displayed %%%superantigen%%% by binding to cell-surface
MHC class II.
AUTHOR: Wung Jay L; Gascoigne Nicholas R J(a)
AUTHOR ADDRESS: (a)Dep. Immunol., Scripps Res. Inst., 10550 North Torrey
Pines Road, La Jolla, CA 92037**USA
JOURNAL: Journal of Immunological Methods 203 (1):p33-41 1997
ISSN: 0022-1759
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We have expressed the %%%superantigen%%% %%%staphylococcal%%%
%%%enterotoxin%%% %%%A%%% (SEA) on the surface of bacteriophage as a
fusion with the gene VIII protein (gVIIIp). This phage-displayed %%%superantigen%%% retains the properties inherent in the natural protein. It binds to MHC class II and activates T-cells bearing appropriate V-beta regions. A flexible 5-amino acid linker sequence between the SEA molecule and the phage coat protein improved the production of functional phage-displayed SEA. Binding to MHC class II-expressing cells effectively selected SEA-phage from non-SEA-phage background. This indicates that this will be an effective method for selecting new specificities of %%%superantigen%%% from libraries of SEA %%%mutants%%% and for cloning of novel %%%superantigens%%%.

7/7/12 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10758526 BIOSIS NO.: 199799379671
T-cell stimulation and cytokine release induced by %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%% (SEA) and the SEAD227A %%%mutant%%%.
AUTHOR: Holzer U; Orlikowsky T; Zehrer C; Bethge W; Dohlsten M; Kalland T;
Niethammer D; Dannecker G E(a)
AUTHOR ADDRESS: (a)Children's Univ. Hosp., Dep. Oncology/Haematology, Ruemelinstr. 23, 72070 Tuebingen**Germany
JOURNAL: Immunology 90 (1):p74-80 1997
ISSN: 0019-2805
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Previous work demonstrated that human cytotoxic T cells activated
by %%%superantigens%%% can lyse major histocompatibility complex (MHC)
class II-positive target cells as well as MHC class II-negative tumour cells coated with conjugates of monoclonal antibodies and %%%superantigens%%%. In order to decrease MHC class II affinity, and therefore unwanted binding of the %%%superantigen%%% %%%staphylococcal%%%
%%%enterotoxin%%% %%%A%%% (SEA) to MHC class II molecules, a point
mutation was introduced into the SEA gene. This mutation (SEAD227A)

resulted in an approximately 3-log reduction of affinity to human leucocyte antigen (HLA)-DR, but cytotoxicity mediated by this %%%mutant%%% %%%superantigen%%% towards antibody-labelled tumour cells is as efficient as cytotoxicity mediated by the native %%%superantigen%%%. We therefore compared the T-cell activating potency of native and mutated SEA. Our data show that SEAD227A is 4- to 5-log less effective than native SEA when activation of resting T cells is assayed in terms of blast formation, expression of cell surface activation markers and cytokine release. Furthermore, presenting either SEA or SEAD227A to MHC class II-negative mononuclear cells by MHC class II-negative tumour cells did not result in significant blast formation of T cells, up-regulation of CD25 or cytokine release. This suggests that lysis of MHC class II-negative tumour cells is efficiently induced by monoclonal antibody targeted %%%superantigen%%%, while activation of resting T cells requires additional co-stimulatory signals.

7/7/13 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10536538 BIOSIS NO.: 199699157683
%%%Superantigen%%% vaccines: A comparative study of genetically attenuated receptor-binding %%%mutants%%% of %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%%.
AUTHOR: Bavari Sina(a); Dyas Beverly; Ulrich Robert G(a)
AUTHOR ADDRESS: (a)Dept. Cell Biol. Biochemistry Molecular Biol. Immunol., AMRIID, Bldg. 1425, Frederick, MD 21702-**USA
JOURNAL: Journal of Infectious Diseases 174 (2):p338-345 1996
ISSN: 0022-1899
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%Superantigens%%% exert their pathologic effects by direct binding to major histocompatibility complex (MHC) class II molecules and T cell antigen receptors (TCR), thus circumventing the normal, antigen-specific immune response. A direct link between disease and toxin suggests an excellent opportunity for vaccine intervention. Site-directed %%%mutants%%% of %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%% (SEA) that have attenuated binding to either the TCR or the MHC class II molecule were developed. Both kinds of SEA %%%mutants%%% induced high levels of antibody against SEA when used as vaccines, and the immunized animals were fully protected when challenged with wild type toxin. However, a residual lethality was associated with the attenuated TCR-binding %%%mutant%%%. These results, combined with an understanding of the molecular nature of %%%superantigen%%% and receptor interactions, indicate that targeting MHC class II binding by site-directed mutagenesis will produce the most effective vaccine.

7/7/14 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10434223 BIOSIS NO.: 199699055368
HLA class II on HIV particles is functional in %%%superantigen%%% presentation to human T cells: Implications for HIV pathogenesis.
AUTHOR: Rossio Jeffrey L(a); Bess Julian Jr; Henderson Louis E; Cresswell Peter; Arthur Larry O
AUTHOR ADDRESS: (a)AIDS Vaccine Program, Program Resources, Inc./DynCorp., Natl. Cancer Inst. Frederick Cancer Res.**USA
JOURNAL: AIDS Research and Human Retroviruses 11 (12):p1433-1439 1995
ISSN: 0889-2229
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The mechanisms of immune suppression by the human immunodeficiency virus, HIV-1, are more complex than simple helper T cell deletion via infection and viral-induced lysis. Since the recent description of cellular proteins associated with HIV suggests that these proteins may be active in viral pathogenesis, the nature of HLA class II gene product carried on HIV, one of the most abundant of the human components carried with the virus, was examined. HIV bearing HLA-DR was shown to act with bacterial %%%superantigen%%%, %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%% (SEA), to stimulate highly purified human T lymphocytes. T cell stimulation by wild-type HIV was shown by both induction of proliferation and by production of the cytokine interleukin 2 (IL-2). In contrast, HIV produced from %%%mutant%%% cells lacking class II genes were unable to cooperate with SEA to activate T cells. Neither whole HIV nor several proteins purified from HIV (gp120, gp41, p24, p7, and p6) exhibited %%%superantigen%%%-like activity in this system. HLA-DR-bearing HIV could, in the continued presence of SEA, induce T cell apoptosis, as detected by nuclear fragmentation and morphological criteria. These data indicate that human cellular proteins associated with HIV may be biologically active, and these proteins should be considered in mechanisms of viral pathogenicity and immunogenicity.

7/7/15 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10273436 BIOSIS NO.: 199698728354
Biochemical and mutational analysis of the histidine residues of %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%%.
AUTHOR: Hoffman Mark(a); Tremaine Mary; Mansfield John; Betley Marsha
AUTHOR ADDRESS: (a)304 Fred Hall, 1550 Linden Dr., Madison, WI 53706**USA
JOURNAL: Infection and Immunity 64 (3):p885-890 1996
ISSN: 0019-9567
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The goal of this study was to examine the role of histidine residues in the biological activities of %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%% (SEA). Carboxymethylated SEA was unable to stimulate murine T-cell proliferation but was resistant to monkey stomach lavage fluid degradation, suggesting that native conformation was intact. Site-directed mutagenesis of the histidine residues of SEA was subsequently performed. SEA-H44A (SEA with histidine 44 replaced with alanine), SEA-H44D, SEA-H50A, SEA-H50D, SEA-H114A, SEA-H114D, SEAH187A, and SEA-H187D retained %%%superantigen%%% and emetic activities, whereas SEA-H225A and SEA-H225D were defective in the ability to stimulate T-cell proliferation. These %%%mutants%%% were unable to compete with SEA for binding to Raji cells, suggesting that the defect in SEA-H225A and SEA-H225D is due to impaired major histocompatibility complex class II binding. SEA-H225D provoked an emetic response in monkeys only if fed at high doses, while SEA-H225A did not provoke an emetic response at low or high doses. In comparison, SEA-H61A and SEA-H61D were defective in emetic activity but not in the ability to stimulate murine T-cell proliferation. Overall, these studies show that the carboxy-terminal histidine at residue position 225 of SEA is important for both the %%%superantigen%%% and emetic activities of this %%%enterotoxin%%%. Histidine 61 appears to be important for emetic activity but not for %%%superantigen%%% activity,

consistent with the hypothesis that the two activities are separable in %%%staphylococcal%%% %%%enterotoxins%%%.

7/7/16 (Item 16 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10194245 BIOSIS NO.: 199698649163
Isolation of HLA-DR1 cntdot (%%%staphylococcal%%% %%%enterotoxin%%% %%%A%%%)-2 trimers in solution.
AUTHOR: Tiedemann R E; Urban R J; Strominger J L; Fraser J D(a)
AUTHOR ADDRESS: (a)Dep. Mol. Medicine, Sch. Medicine, Univ. Auckland, Auckland**New Zealand
JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 92 (26):p12156-12159 1995
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Mutational studies indicate that the %%%superantigen%%% %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%% (SEA) has two separate binding sites for major histocompatibility complex (MHC) class II molecules. Direct evidence is provided here for the formation of SEA-MHC class II trimers in solution. Isoelectric focusing separated SEA-HLA-DR1 complexes into both dimers and HLA-DR1-SEA2 trimers. The molar ratio of components was determined by dual isotope labeling. The SEA %%%mutant%%% SEA-F47S, L48S, Y92A, which is deficient in MHC class II alpha-chain binding, formed only dimers with HLA-DR1, whereas a second SEA %%%mutant%%%, SEA-H225A, which lacks high-affinity MHC class II beta-chain binding was incapable of forming any complexes. Thus SEA binding to its MHC receptor is a two-step process involving initial beta-chain binding followed by cooperative binding of a second SEA molecule to the class II a chain.

7/7/17 (Item 17 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10095218 BIOSIS NO.: 199598550136
Antibodies are capable of directing %%%superantigen%%%-mediated T cell killing of chronic B lymphocytic leukemia cells.
AUTHOR: Gidlof C; Dohlsten M; Kalland T; Totterman T H(a)
AUTHOR ADDRESS: (a)Dep. Clinical Immunol., Univ. Hosp., S-751 85 Uppsala** Sweden
JOURNAL: Leukemia (Basingstoke) 9 (9):p1534-1542 1995
ISSN: 0887-6924
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The bacterial %%%superantigen%%% %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%% (SEA) is a highly potent activator of cytotoxic T cells when presented on MHC class II molecules of target cells. Our earlier studies showed that such SEA-directed T cells efficiently killed chronic B lymphocytic leukemia (B-CLL) cells. With the ultimate goal to replace the natural specificity of SEA for MHC class II molecules with the specificity of a monoclonal antibody (mAb), we initially made a mutated protein A-SEA (PA-SEAm) fusion protein with gt 100-fold reduced binding affinity for MHC class II compared to native SEA. The fusion protein was successfully used to direct T cells to B-CLL cells coated with different B lineage specific (CD19, CD20) or associated (CD37, CD40) mAbs. The PA-SEAm protein was 10-100-fold more potent against mAb coated compared to uncoated HLA class II+ B-CLL cells. No correlation was seen between the amount of mAb bound to the cell surface and sensitivity to lysis. Preactivation of B-CLL cells by phorbol ester increased their sensitivity, and lysis was dependent on ICAM-1 molecules. However, no preactivation of the target cells was needed when a cocktail of two or four mAbs was used. Circulating leukemia and spleen cells were equally well killed. We conclude that the natural target specificity of SEA, MHC class II, can be reduced by mutagenesis and novel binding specificity can be introduced by linkage to tumor reactive mAbs. Our findings encourage the construction of recombinant SEA %%%mutant%%% fusion proteins for specific T cell therapy of hematopoietic tumors such as B-CLL.

7/7/18 (Item 18 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09953241 BIOSIS NO.: 199598408159
Characterization of two distinct MHC class II binding sites in the %%%superantigen%%% %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%%.
AUTHOR: Abrahmsen Lars; Dohlsten Mikael(a); Segren Sverker; Bjork Per; Jonsson Elisabet; Kalland Terje
AUTHOR ADDRESS: (a)Pharmacia Oncol. Immunol., Box 724, S-220 07 Lund** Sweden
JOURNAL: EMBO (European Molecular Biology Organization) Journal 14 (13):p 2978-2986 1995
ISSN: 0261-4189
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Bacterial %%%superantigens%%% (SAgs) are potent activators of T lymphocytes and play a pathophysiological role in Gram-positive septic shock and food poisoning. To characterize potential MHC class II binding sites of the bacterial SAg %%%staphylococcal%%% %%%enterotoxin%%% (SE) A, we performed alanine substitution mutagenesis throughout the C-terminus and at selected sites in the N-terminal domain. Four amino acids in the C-terminus were shown to be involved in MHC class II binding. Three of these amino acids, H225, D227 and H187, had a major influence on MHC class 11 binding and appeared to be involved in coordination of a Zn-2+ ion. Alanine substitution of H225 and D227 resulted in a 1000-fold reduction in MHC class II affinity. Mutation at F47, which is equivalent to the F44 previously shown to be central in the MHC class II binding site of the SAg SEB, resulted in a 10-fold reduction in MHC class II affinity. The combination of these mutations in the N- and C-terminal sites resulted in a profound loss of activity. The perturbation of MHC class II binding in the various %%%mutants%%% was accompanied by a corresponding loss of ability to induce MHC class II-dependent T cell proliferation and cytotoxicity. All of the SEA %%%mutants%%% were expressed as Fab-SEA fusion proteins and found to retain an intact T cell receptor (TCR) epitope, as determined in a mAb targeted MHC class II-independent T cell cytotoxicity assay. We propose a model in which the N- and C-terminal sites in SEA cooperate to form a high affinity interaction which involves binding to two separate MHC class II molecules. Considering the previously described SEB-HLA-DR complex, this study indicates that SAgs may bind monovalently or bivalently to MHC class II molecules and could be presented to the TCR as a dimeric or trimeric complex.

7/7/19 (Item 19 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09922077 BIOSIS NO.: 199598376995
Transcriptional activation of the human TNF-alpha promoter by %%%superantigen%%% in human monocytic cells: Role of NF-kappa-B.
AUTHOR: Trede Nikolaus S(a); Tsytsykova Alla V; Chatila Talal; Goldfeld Anne E; Geha Raif S
AUTHOR ADDRESS: (a)Div. Immunol., Children's Hosp., 300 Longwood Ave., Boston, MA 02115**USA
JOURNAL: Journal of Immunology 155 (2):p902-908 1995
ISSN: 0022-1767
DOCUMENT TYPE: Article

Jeffrey L
; Davis Mark M; Chien Yueh-Hsiu(a)
AUTHOR ADDRESS: (a)Dep. Microbiol. Immunol., Stanford Univ., Stanford, CA
94305**USA
JOURNAL: Journal of Experimental Medicine 178 (2):p713-722 1993
ISSN: 0022-1007
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: While recent evidence strongly suggests that the third complementarity determining regions (CDR3s) of T cell receptors (TCRs) directly contact antigenic peptides bound to major histocompatibility complex (MHC) molecules, the nature of other TCR contact(s) is less clear. Here we probe the extent to which different antigens can affect this interaction by comparing the responses of T cells bearing structurally related TCRs to cytochrome c peptides and %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%% (SEA) presented by 13
%%%mutant%%% antigen-presenting cell (APC) lines. Each APC expresses a class II MHC molecule (I-E-k) with a single substitution of an amino acid residue predicted to be located on the MHC alpha helices and to point "up" towards the TCR. We find that very limited changes (even a single amino acid) in either a CDR3 loop of the TCR or in a contact residue of the antigenic peptide can have a profound effect on relatively distant TCR/MHC interactions. The extent of these effects can be as great as that
observed between T cells bearing entirely different TCRs and recognizing different peptides. We also find that %%%superantigen%%% presentation entails a distinct mode of TCR/MHC interaction compared with peptide presentation. These data suggest that TCR/MHC contacts can be made in a variety of ways between the same TCR and MHC, with the final configuration apparently dominated by the antigen. These observations suggest a molecular basis for recent reports in which either peptide analogues or %%%superantigens%%% trigger distinct pathways of T cell activation.

7/7/23 (Item 23 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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08402955 BIOSIS NO.: 000094120609
PP59F-Y-N %%%MUTANT%%% MICE DISPLAY DIFFERENTIAL SIGNALING IN THYMOCYTES
AND PERIPHERAL T CELLS
AUTHOR: STEIN P L; LEE H-M; RICH S; SORIANO P
AUTHOR ADDRESS: INST. MOLECULAR GENETICS, BAYLOR COLL. MED., HOUSTON, TEXAS
77030.
JOURNAL: CELL 70 (5). 1992. 741-750. 1992
FULL JOURNAL NAME: Cell
CODEN: CELLB
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: We have generated %%%mutant%%% mice that do not express pp59fyn,
a nonreceptor protein tyrosine kinase related to pp60src, by homologous recombination in embryonic stem cells. fyn- mice did not display an overt phenotype. Because fyn is associated with the T cell receptor (TCR), thymocyte and T cell signaling was analyzed in the %%%mutant%%% background. Cross-linking of TCR-CD3 in thymocytes led to markedly reduced calcium fluxes and abrogated proliferation, whereas mature splenic T cells retained largely normal proliferation despite depressed calcium movements and IL-2 production. Similarly, proliferation induced by Thy-1 cross-linking was reduced in thymocytes but not in splenic T cells. fyn- thymocytes were impaired at a late stage of maturation and showed limited clonal deletion to the Mls-1a self-%%%superantigen%%% but
not to %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%%. These results
implicate fyn as a critical component in TCR signaling in thymocytes and, potentially, in the progress that determines T cell repertoire in the adult mouse.

7/7/24 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2003 Inst for Sci Info. All rts. reserv.

11538095 Genuine Article#: 664AL Number of References: 52
Title: Crystal structure of a SEA %%%variant%%% in complex with MHC class
II reveals the ability of SEA to crosslink MHC molecules
Author(s): Petersson K; Thunnissen M; Forsberg G; Walse B (REPRINT)
Corporate Source: Act Biotech Res AB,POB 724/S-22007 Lund//Sweden/ (REPRINT); Act Biotech Res AB,S-22007 Lund//Sweden/; Lund Univ,Ctr Chem
& Chem Engn,S-22100 Lund//Sweden/
Journal: STRUCTURE, 2002, V10, N12 (DEC), P1619-1626
ISSN: 0969-2126 Publication date: 20021200
Publisher: CELL PRESS, 1100 MASSACHUSETTS AVE, CAMBRIDGE, MA 02138 USA
Language: English Document Type: ARTICLE
Abstract: Although the biological properties of %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%% (SEA) have been well characterized, structural insights into the interaction between SEA and major histocompatibilty complex (MHC) class II have only been obtained by modeling. Here, the crystal structure of the D227A %%%variant%%% of SEA
in complex with human MHC class II has been determined by X-ray crystallography. SEA(D227A) exclusively binds with its N-terminal domain to the alpha chain of HLA-DR1. The ability of one SEA molecule to crosslink two MHC molecules was modeled. It shows that this SEA molecule cannot interact with the T cell receptor (TCR) while a second SEA molecule interacts with MHC. Because of its relatively low toxicity, the D227A %%%variant%%% of SEA is used in tumor therapy.

7/7/25 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2003 Inst for Sci Info. All rts. reserv.

10412657 Genuine Article#: 523BR Number of References: 54
Title: Structural basis for abrogated binding between %%%staphylococcal%%%
%%%enterotoxin%%% %%%A%%% %%%superantigen%%% vaccine and MHC-II alpha
Author(s): Krupka HI; Segelke BW; Ulrich RG; Ringhofer S; Knapp M; Rupp B (REPRINT)
Corporate Source: Lawrence Livermore Natl Lab,LLNL, BBRP,POB 808,L-448/Livermore//CA/94551 (REPRINT); Lawrence Livermore Natl Lab,Macromol Crystallog Biol & Biotechnol Res Program,Livermore//CA/94551; USA,Med Res Inst Infect Dis, Lab Mol Immunol,Frederick//MD/21702
Journal: PROTEIN SCIENCE, 2002, V11, N3 (MAR), P642-651
ISSN: 0961-8368 Publication date: 20020300
Publisher: COLD SPRING HARBOR LAB PRESS, 1 BUNGTOWN RD, PLAINVIEW, NY 11724
USA
Language: English Document Type: ARTICLE
Abstract: %%%Staphylococcal%%% %%%enterotoxins%%% (SEs) are %%%superantigenic%%% protein toxins responsible for a number of life-threatening diseases. The X-ray structure of a %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%% (SEA) triple-%%%mutant%%% (L48R, D70R, and Y92A) vaccine reveals a cascade of structural rearrangements located in three loop regions essential for binding the alpha subunit of major histocompatibility complex class II (MHC-II) molecules. A comparison of hypothetical model complexes between SEA and the SEA triple %%%mutant%%% with MHC-II HLA-DR1 clearly
shows disruption of key ionic and hydrophobic interactions necessary for forming the complex. Extensive dislocation of the disulfide loop in particular interferes with MHC-IIalpha binding. The triple-%%%mutant%%%
structure provides new insights into the loss of %%%superantigenicity%%% and toxicity of an engineered %%%superantigen%%% and provides a basis for further design of %%%enterotoxin%%% vaccines.

7/7/26 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2003 Inst for Sci Info. All rts. reserv.

10201429 Genuine Article#: 496TR Number of References: 28
Title: Cooperative zinc binding in a %%%staphylococcal%%% %%%enterotoxin%%%
%%%A%%% %%%mutant%%% mimics the SEA-MHC class II interaction
Author(s): Hakansson M (REPRINT) ; Antonsson P; Bjork P; Svensson LA
Corporate Source: Ctr Chem & Chem Engn,Dept Mol Biophys,POB 124/S-22100
Lund//Sweden/ (REPRINT); Ctr Chem & Chem Engn,Dept Mol Biophys,S-22100
Lund//Sweden/; Act Biotech Res AB,Dept Biochem & Mol Biol,S-22007 Lund//Sweden/
Journal: JOURNAL OF BIOLOGICAL INORGANIC CHEMISTRY, 2001, V6, N8 (OCT), P
757-762
ISSN: 0949-8257 Publication date: 20011000
Publisher: SPRINGER-VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010 USA
Language: English Document Type: ARTICLE
Abstract: The structure of a %%%mutant%%% form of %%%staphylococcal%%%
%%%enterotoxin%%% %%%A%%% (SEA) has been determined to 2.1 Angstrom
resolution. The studied SEA substitution H187 --> A187 (SEA(H187A)) leads to an almost 110-fold reduction of the binding to major histocompatibility complex (MHC) class II. H187 is important for this interaction since it coordinates Zn2+. The zinc ion is thought to hold MHC class II and SEA together in a complex. Interestingly, only one of two molecules in the asymmetric unit binds Zn2+. H225, D227, a water molecule, and H44 from a symmetry-related molecule ligate Zn2+. The symmetry-related histidine is necessary for this substituted Zn2+ site to bind to Zn2+ at low zinc concentration (no Zn2+ added). Since a water Molecule replaces the missing H187, H44 binds Zn2+ at the position where beta H81 frorm MHC class II probably will bind. Dynamic light scattering analysis reveals that in solution as well as in the crystal lattice the SEA(H187A) %%%mutant%%% forms aggregates. The substitution per se does not cause aggregation since wild-type SEA also forms aggregates. Addition of EDTA reduces the size of the aggregates, indicating a cross-linking function of Zn2+. In agreement with the biological function, the aggregation is weak (i.e. not revealed by gel filtration,) and non-specific.

7/7/27 (Item 4 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2003 Inst for Sci Info. All rts. reserv.

09697292 Genuine Article#: 436AQ Number of References: 31
Title: Structural features of a zinc binding site in the %%%superantigen%%%
streptococcal pyrogenic exotoxin A (SpeA1): Implications for MHC class IT recognition
Author(s): Baker M; Gutman DM; Papageorgiou AC; Collins CM; Acharya KR (REPRINT)
Corporate Source: Univ Bath,Dept Biol & Biochem,South Bldg,Claverton Down/Bath BA2 7AY/Avon/England/ (REPRINT); Univ Bath,Dept Biol & Biochem,Bath BA2 7AY/Avon/England/; Univ Miami,Sch Med, Dept Microbiol
& Immunol,Miami//FL/33101
Journal: PROTEIN SCIENCE, 2001, V10, N6 (JUN), P1268-1273
ISSN: 0961-8368 Publication date: 20010600
Publisher: COLD SPRING HARBOR LAB PRESS, 1 BUNGTOWN RD, PLAINVIEW, NY 11724
USA
Language: English Document Type: ARTICLE
Abstract: Streptococcal pyrogenic exotoxin A (SpeA) is produced by Streptococcus pyogenes, and has been associated with severe infections such as scarlet fever and Streptococcal Toxic Shock Syndrome (STSS). In
this study, the crystal structure of SpeA1 (the product of speA allele 1) in the presence of 2.5 mM zinc was determined at 2.8 Angstrom resolution. The protein crystallizes in the orthorhombic space group P2(1)2(1)2, with four molecules in the crystallographic asymmetric unit. The final structure has a crystallographic R-factor of 21.4% for 7,031 protein atoms, 143 water molecules, and 4 zinc atoms tone zinc atom per molecule). Four protein ligands-Glu 33, Asp 77, His 106, and His 110-form a zinc binding site that is similar to the one observed in a related %%%superantigen%%%, %%%staphylococcoal%%% %%%enterotoxin%%%
C2. %%%Mutant%%% toxin forms substituting Ala for each of the zinc binding residues were generated. The affinity of these %%%mutants%%% for zinc ion confirms the composition of this metal binding site. The implications of zinc binding to SpeA1 for MHC class ii recognition are explored using a molecular modeling approach. The results indicate that, despite their common overall architecture, %%%superantigens%%% appear to have multiple ways of complex formation with MHC class II molecules.

7/7/28 (Item 5 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2003 Inst for Sci Info. All rts. reserv.

09559095 Genuine Article#: 419QE Number of References: 84
Title: %%%Superantigen%%% recognition by gamma delta T cells: SEA recognition site for human V gamma 2 T cell receptors
Author(s): Morita CT (REPRINT) ; Li HM; Lamphear JG; Rich RR; Fraser JD; Mariuzza RA; Lee HK
Corporate Source: Univ Iowa,Coll Med, Dept Internal Med, Div Rheumatol,Iowa
City//IA/52242 (REPRINT); Univ Iowa,Coll Med, Dept Internal Med, Div Rheumatol,Iowa City//IA/52242; Univ Iowa,Coll Med, Interdisciplinary Grp Immunol,Iowa City//IA/52242; Univ Maryland,Inst Biotechnol, Ctr Adv
Res Biotechnol,Rockville//MD/20850; Baylor Coll Med,Dept Microbiol & Immunol,Houston//TX/77030; Emory Univ,Sch Med, Dept Med Microbiol &
Immunol,Atlanta//GA/30322; Univ Auckland,Sch Med, Dept Mol Med,Auckland
1//New Zealand/
Journal: IMMUNITY, 2001, V14, N3 (MAR), P331-344
ISSN: 1074-7613 Publication date: 20010300
Publisher: CELL PRESS, 1100 MASSACHUSETTES AVE,, CAMBRIDGE, MA 02138 USA
Language: English Document Type: ARTICLE
Abstract: Human gamma delta T cells expressing the V gamma 2V delta2 antigen receptors recognize nonpeptide prenyl pyrophosphate and alkylamine antigens. We find that they also recognize %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%% %%%superantigens%%% in a
manner distinct from the recognition of nonpeptide antigens. Using chimeric and %%%mutant%%% toxins, SEA amino acid residues 20-27 were
shown to be required for gamma delta TCR recognition of SEA. Residues at 200-207 that are critical for specific alpha beta TCR recognition of SEA do not affect gamma delta TCR recognition. SEA residues 20-27 are located in an area contiguous with the binding site of V beta chains. This study defines a %%%superantigen%%% recognition site for a gamma delta T cell receptor and demonstrates the differences between V gamma 2V delta2(+) T cell recognition of %%%superantigens%%% and nonpeptide antigens.

7/7/29 (Item 6 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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09405076 Genuine Article#: 400QA Number of References: 58
Title: Diverse repertoire of the MHC class II-peptide complexes is required for presentation of viral %%%superantigens%%%
Author(s): Golovkina TV (REPRINT) ; Agafonova Y; Kazansky D; Chervonsky A
Corporate Source: Jackson Lab,600 Main St/Bar Harbor//ME/04609 (REPRINT);
Jackson Lab,Bar Harbor//ME/04609; Canc Res Ctr,Inst Carcinogensis,Moscow//Russia/
Journal: JOURNAL OF IMMUNOLOGY, 2001, V166, N4 (FEB 15), P2244-2250
ISSN: 0022-1767 Publication date: 20010215

many target depending on repr

Publisher: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA, MD
20814 USA
Language: English Document Type: ARTICLE
Abstract: Among other features, peptides affect MHC class II molecules, causing changes in the binding of bacterial %%%superantigens%%% (b-Sag), Whether peptides can alter binding of viral %%%superantigens%%% (v-Sag) to MHC class II was not known. Here we addressed the question of whether mutations limiting the diversity of peptides bound by the MHC class II molecules influenced the presentation of v-Sag and, subsequently; the life cycle of the mouse mammary tumor virus (MMTV). T cells reactive to v-Sag were found in mice lacking DM molecules as well as in A(b)Ep-transgenic mice in which MHC class II binding grooves were predominantly occupied by an invariant chain fragment or E alpha (52-68) peptide, respectively, APCs from the %%%mutant%%% mice failed to present v-Sag, as determined by
the lack of Sag-specific T cell activation, Sag-induced T cell deletion, and by the aborted MMTV infection. In contrast, mice that express I-A(b) with a variety of hound peptides presented v-Sag and were susceptible to MMTV infection. Comparison of v-Sag and b-Sag presentation by the same %%%mutant%%% cells suggested that presentation
of v-Sag had requirements similar to that for presentation of toxic shock syndrome toxin-1. Thus, MHC class II peptide repertoire is critical for recognition of v-Sag by the T cells and affects the outcome of infection with a retrovirus.

7/7/30 (Item 7 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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07819766 Genuine Article#: 211WZ Number of References: 35
Title: %%%Staphylococcus%%% aureus isogenic %%%mutant%%%, deficient in
toxic shock syndrome toxin-1 but not %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%% production, exhibits attenuated virulence in
a tampon-associated vaginal infection model of toxic shock syndrome
Author(s): DeBoer ML; Kum WWS; Chow AW (REPRINT)
Corporate Source: VANCOUVER HOSP HLTH SCI CTR,DIV INFECT DIS, GF STRONG RES
LABS, 2733 HEATHER ST/VANCOUVER/BC V5Z 3J5/CANADA/ (REPRINT); VANCOUVER
HOSP HLTH SCI CTR,DIV INFECT DIS, GF STRONG RES LABS/VANCOUVER/BC V5Z
3J5/CANADA/; UNIV BRITISH COLUMBIA,DIV INFECT DIS, DEPT MED/VANCOUVER/BC V5Z 1M9/CANADA/; UNIV BRITISH COLUMBIA,DIV INFECT DIS,
DEPT IMMUNOL & MICROBIOL/VANCOUVER/BC V5Z 1M9/CANADA/; CANADIAN
BACTERIAL DIS NETWORK,/VANCOUVER/BC/CANADA/
Journal: CANADIAN JOURNAL OF MICROBIOLOGY, 1999, V45, N3 (MAR), P250-256
ISSN: 0008-4166 Publication date: 19990300
Publisher: NATL RESEARCH COUNCIL CANADA, RESEARCH JOURNALS, MONTREAL RD,
OTTAWA ON K1A 0R6, CANADA
Language: English Document Type: ARTICLE
Abstract: Since menstrual toxic shock syndrome (MTSS)is associated with a predominant clone of %%%Staphylococcus%%% aureus which produces both
toxic shock syndrome toxin-1 (TSST-1) and %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%% (SEA), we sought to clarify the role of TSST-1 in a tampon-associated vaginal infection model in New Zealand White (NZW) rabbits, using isogenic tst(+)/sea(+) S. aureus %%%mutants%%% in which rst was inactivated by allelic replacement. Rabbits infected with the tst(-)/sea(+) strain became ill within 3 days, with fever, weight loss, conjunctival hyperemia, and lethargy. Mortality was significantly higher with the tst(+)/sea(+) strain compared to its tst(-)/sea(+) isogenic derivative (4/13 vs. 0/14; p < 0.05, Fisher's exact test, 2-tailed). Mean fever index was higher (p < 0.005; t test, 2-tailed) and weight loss more sustained among survivors in the tst(+)/sea(+) group. Furthermore, culture filtrates from the tst(+)/sea(+) strain induced a significantly greater response in mitogenesis and TNF alpha secretion from rabbit splenocytes in vitro compared to the tst(-)/sea(+) isogenic derivative. Thus, regardless of the role of SEA, TSST-1 significantly contributed to both morbidity and mortality in this tampon-associated vaginal infection model in NZW rabbits. This is the first demonstration of the potential role of TSST-1 and SEA in the pathogenesis of MTSS with a MTSS-associated clinical S. aureus strain in a relevant animal model.

7/7/31 (Item 8 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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07035522 Genuine Article#: 117DT Number of References: 35
Title: MHC class II-independent, V beta-specific activation of T cells by %%%superantigen%%% %%%mutants%%% fused to anti-tumor F-ab fragments:
Implications for use in treatment of human colon carcinoma
Author(s): Newton DW; Dohlsten M; Lando PA; Kalland T; Olsson C; Kotb M (REPRINT)
Corporate Source: DEPT VET AFFAIRS MED CTR,RES SERV, 1030 JEFFERSN
AVE/MEMPHIS//TN/38104 (REPRINT); DEPT VET AFFAIRS MED CTR,RES
SERV/MEMPHIS//TN/38104; UNIV TENNESSEE,DEPT SURG/MEMPHIS//TN/38163;
UNIV TENNESSEE,DEPT MICROBIOL & IMMUNOL/MEMPHIS//TN/38163; PHARMACIA &
UPJOHN AB,LUND RES CTR/S-22363 LUND//SWEDEN/; LUND UNIV,DEPT CELL & MOL
BIOL/LUND//SWEDEN/
Journal: INTERNATIONAL JOURNAL OF MOLECULAR MEDICINE, 1998, V1, N1 (JAN), P
157-162
ISSN: 1107-3756 Publication date: 19980100
Publisher: INT JOURNAL MOLECULAR MEDICINE, 1, S MERKOURI ST, ATHENS 116 35,
GREECE
Language: English Document Type: ARTICLE
Abstract: Genetically engineered fusion proteins of the %%%superantigen%%%
%%%staphylococcal%%% %%%enterotoxin%%% %%%A%%% (SEA) and tumor-reactive
monoclonal antibodies, C215F(ab)-SEA and C242F(ab)-SEA, have been generated and shown to be effective in mediating %%%superantigen%%% -antibody directed cellular cytotoxicity against human carcinoma cells expressing the CA215 or CA242 antigens in an MHC class II-independent manner. In an attempt to reduce the in vivo toxicity of %%%superantigen%%% administration, alanine substitution mutations in SEA at residues F47 and D227 that affect SEA binding to class II molecules have been created and genetically linked to C215F(ab) or C242F(ab). The purpose of this study was to determine whether these F-ab-SEA %%%mutant%%% fusion proteins, that have low MHC class II binding affinities, were still able to stimulate human T cells in a V beta-specific manner in the presence or absence of MHC class II molecules. The SEA wt- and SEA-D227A-based fusion proteins shared the
ability to activate V beta 5.2-, V beta 6-, V beta 7-, V beta 9- and V beta 18-bearing T cells, whereas F-ab-SEA-F47A protein activated only V beta 6- and V beta 7-bearing T cells. The fusion of F-ab fragments onto SEA wt, SEA-F47A or SEA-D227A had no effect on the V beta specificity
of these %%%superantigens%%%. F-ab fusion proteins containing either SEA wt or SEA %%%mutants%%% were presented, in the absence of class II
molecules, by CHO cells transfected with CA215 and CD80 and all induced the expansion of only V beta 6-, V beta 7- and V beta 18-bearing T cells. F-ab-SEA %%%mutant%%% fusion proteins may provide attenuated therapeutic agents that, while still able to specifically target high affinity T cells for MHC class II-independent local tumor killing, will not induce excessive systemic toxicity.

7/7/32 (Item 9 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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06829118 Genuine Article#: ZV227 Number of References: 42
Title: Induction of acute inflammation in vivo by %%%staphylococcal%%% %%%superantigens%%% I: Leukocyte recruitment occurs independently of T
lymphocytes and major histocompatibility complex class II molecules
Author(s): Diener K; Tessier P; Fraser J; Kontgen F; McColl SR (REPRINT)
Corporate Source: UNIV ADELAIDE,DEPT MICROBIOL & IMMUNOL, MOL INFLAMMAT
LAB, FROME RD/ADELAIDE/SA 5005/AUSTRALIA/ (REPRINT); UNIV ADELAIDE,DEPT
MICROBIOL & IMMUNOL, MOL INFLAMMAT LAB/ADELAIDE/SA 5005/AUSTRALIA/;
UNIV AUCKLAND,SCH MED, DEPT MOL MED/AUCKLAND//NEW ZEALAND/; ROYAL
MELBOURNE HOSP,WALTER & ELIZA HALL INST MED RES, SINGLE CELL LAB,
CELLULAR IMMUNOL UNIT/MELBOURNE/VIC/AUSTRALIA/
Journal: LABORATORY INVESTIGATION, 1998, V78, N6 (JUN), P647-656
ISSN: 0023-6837 Publication date: 19980600
Publisher: WILLIAMS & WILKINS, 351 WEST CAMDEN ST, BALTIMORE, MD 21201-2436
Language: English Document Type: ARTICLE
Abstract: Studies in our laboratory and others have recently shown that %%%staphylococcal%%% %%%enterotoxin%%%-derived %%%superantigens%%%
stimulate proinflammatory cytokine gene expression in vitro. We have therefore investigated the ability of %%%superantigens%%% to induce leukocyte accumulation at extravascular sites in vivo using the subcutaneous air pouch model. Injection of %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%% (SEA) induced a significant accumulation of
leukocytes over basal levels in a time- and dose-dependent manner. It was also shown that %%%superantigens%%% are capable of inducing this response in mice depleted of CD4(+) T cells, as well as in severe combined immune-deficient and nude mice. These observations suggest that %%%superantigens%%% are capable of inducing leukocyte accumulation
independently of the presence of T lymphocytes. Experiments were also conducted using %%%mutant%%% SEAs that have a reduced binding affinity
for major histocompatibility complex (MHC) Class II molecules, as well as using MHC Class II-deficient mice. The results of these experiments indicated that MHC Class II molecules are not required for the observed effect of %%%superantigens%%% in vivo. Taken together, these results indicate, first, that bacterial %%%superantigens%%% promote inflammation in subcutaneous tissue in vivo and, second, the potential existence of a novel receptor for %%%superantigens%%% that mediates this subcutaneous inflammatory response.

7/7/33 (Item 10 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2003 Inst for Sci Info. All rts. reserv.

06696894 Genuine Article#: ZL317 Number of References: 38
Title: Man-made %%%superantigens%%%: Tumor-selective agents for T-cell-based therapy
Author(s): Brodin TN (REPRINT) ; Persson R; Soegaard M; Ohlsson L; dArgy R;
Olsson J; Molander A; Antonsson P; Gunnarsson PO; Kalland T; Dohlsten M
Corporate Source: PHARMACIA & UPJOHN INC,RES CTR, SCHEELEVAGEN 22/S-22363
LUND//SWEDEN/ (REPRINT)
Journal: ADVANCED DRUG DELIVERY REVIEWS, 1998, V31, N1-2 (APR 6), P131-142
ISSN: 0169-409X Publication date: 19980406
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS
Language: English Document Type: REVIEW
Abstract: %%%Superantigens%%% (SAgs) are a collection of bacterial and viral proteins with potent immunostimulatory properties. SAgs bind to Major Histocompatibility Complex Class II (MHC II) molecules of antigen presenting cells (APCs) and activate a high frequency of T lymphocytes. To target a T-cell attack against tumor cells we genetically linked tumor-specific antibody Fas fragments to the SAg %%%Staphylococcal%%% %%%enterotoxin%%% %%%A%%% (SEA). Fab-SEA fusion protein efficiently
targeted to solid tumors and induced a T-cell-mediated eradication of established metastases in animal models. Successful therapy was T-cell-dependent and required tumor specificity of the Fas moiety of the Fab-SEA fusion protein. Due to the high affinity of SAg for MHC II, a limitation of this approach was retention of Fab-SEA proteins in normal tissues expressing MHC II, which caused systemic immune activation and dose limiting toxicity. We recently solved the structure of SEA and applied structure-based drug design to develop a novel generation of 'man-made' SAg with improved pharmacological and pharmacokinetic properties, Mutation of the major MHC II binding site of SEA substantially reduced retention in MHC II; tissues and systemic toxicity, while local immune activation at targeted tumor sites was retained. The FLU-SEA %%%mutants%%% display a 10 000-fold higher affinity for tumor tissue compared to normal tissue and the therapeutic window was improved > 100-fold compared to native Fab-SEA protein, Thus
protein engineering can be applied to convert harmful bacterial toxins into tolerable tumor-specific agents. (C) 1998 Elsevier Science B.V.

7/7/34 (Item 11 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2003 Inst for Sci Info. All rts. reserv.

06681553 Genuine Article#: ZK231 Number of References: 46
Title: Quantitative defect in %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%% binding and presentation by HLA-DM-deficient T2.A(k) cells corrected by transfection of HLA-DM genes
Author(s): Albert LJ (REPRINT) ; Denzin LK; Ghumman B; Bangia N; Cresswell P; Watts TH
Corporate Source: ONTARIO CANC INST,DEPT MED BIOPHYS, 610 UNIV AVE/TORONTO/ON M5G 2M9/CANADA/ (REPRINT); UNIV TORONTO,DEPT IMMUNOL/TORONTO/ON M5S 1A8/CANADA/; YALE UNIV,SCH MED, IMMUNOBIOL SECT, HOWARD HUGHES MED INST/NEW HAVEN//CT/06510
Journal: CELLULAR IMMUNOLOGY, 1998, V183, N1 (JAN 10), P42-51
ISSN: 0008-8749 Publication date: 19980110
Publisher: ACADEMIC PRESS INC JNL-COMP SUBSCRIPTIONS, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495
Language: English Document Type: ARTICLE
Abstract: HLA-DM facilitates peptide acquisition by MHC class II proteins within the endosomes of APC by facilitating release of invariant chain peptide intermediates (CLIP) from the class II molecules. T2 cells have a deletion in the MHC II region which deletes HLA-DM and MHC II genes.
T2 cells transfected with MHC class II proteins are defective in protein presentation, a defect that is corrected by HLA-DM transfection. Here we show that T2 cells transfected with A(k) are also impaired in binding and presentation of the %%%superantigen%%% staphyococcal %%%enterotoxin%%% %%%A%%% and that HLA-DM transfection
corrects this defect. The poor ability of SEA to bind to A(k) on DM-deficient cells is somewhat surprising since A(k) has a low affinity for CLIP and is not predominantly occupied with CLIP on T2 cells compared to wild-type APC. These data suggest an influence of HLA-DM on
the structure or composition of the A(k)/peptide complex beyond its role in the release of invariant chain peptides. (C) 1998 Academic Press.

7/7/35 (Item 12 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2003 Inst for Sci Info. All rts. reserv.

06321432 Genuine Article#: YJ227 Number of References: 41
Title: A mutation of F47 to A in %%%staphylococcus%%% %%%enterotoxin%%% %%%A%%% activates the T-cell receptor V beta repertoire in vivo
Author(s): Rosendahl A; Hansson J; Antonsson P; Sekaly RP; Kalland T;

Dohlsten M (REPRINT)
Corporate Source: PHARMACIA & UPJOHN INC,CTR LUNG RES, BOX 724/S-22007
LUND//SWEDEN/ (REPRINT); LUND UNIV,DEPT CELL & MOL BIOL/LUND//SWEDEN/;
INST RECH CLIN MONTREAL,IMMUNOL LAB/MONTREAL/PQ H2W 1R7/CANADA/; UNIV
MONTREAL,FAC MED, DEPT MICROBIOL & IMMUNOL/MONTREAL/PQ H3C 3J7/CANADA/
Journal: INFECTION AND IMMUNITY, 1997, V65, N12 (DEC), P5118-5124
ISSN: 0019-9567 Publication date: 19971200
Publisher: AMER SOC MICROBIOLOGY, 1325 MASSACHUSETTS AVENUE, NW,
WASHINGTON, DC 20005-4171
Language: English Document Type: ARTICLE
Abstract: The bacterial %%%superantigen%%% %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%% (SEA) binds with high affinity to major
histocompatibility complex (MHC) class II molecules and subsequently activates T cells bearing particular T-cell receptor (TCR) V beta chains, Structural and mutational studies have defined two distinct MHC class II binding sites located in the N-terminal and C-terminal domains of SEA. The N-terminal F47 amino acid is critically involved in a low-affinity interaction to the MHC class II alpha-chain, while the C-terminal residues H187, H225, and D227 coordinate a Zn2+ ion and bind with moderate affinity to the beta-chain. In order to analyze whether the SEA-MHC class II alpha-chain interaction plays a role in dictating the in vivo repertoire of T-cell subsets, rye studied distinct V beta populations after stimulation with wild-type SEA [SEA((wt))] and SEA with an F47A mutation [SEA((F47A))]. Injections of SEA((wt)) in C57BL/6
mice induced cytokine release in serum, strong cytotoxic T-lymphocyte activity, expansion of T-cell subsets, and modulated expression of the T-cell activation antigens CD25, CD11a, CD44, CD62L, and CD69. SEA-reactive TCR V beta 3(+) and V beta 11(+) T cells were activated, while TCR V beta 8(+) T cells remained unaffected. The SEA((F47A)) %%%mutant%%% protein induced a weaker T-cell response and failed to induce substantial interleukin-6 production compared to SEA((wt)). Notably, SEA((F47A)) failed to activate TCR V beta 11(+) T cells, whereas in vivo expansion and modulation of T-cell activation markers on TCR V beta 3(+) T cells were similar to those for SEA((wt)). A similar response to SEA((F47A)) was seen among CD4+ and CD8+ T cells. Activation of TCR V beta 3(+) and TCR V beta 11(+) T-cell hybridomas confirmed that SEA((F47A)) activates TCR V beta 3(+) but not TCR V beta
11(+) T cells. The data support the view that the SEA-N-terminal MHC class II alpha-chain interaction defines a topology that is required for engagement of certain TCR V beta chains in vivo.

7/7/36 (Item 13 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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05772190 Genuine Article#: WX141 Number of References: 33
Title: Tumor therapy with an antibody-targeted %%%superantigen%%% generates
a dichotomy between local and systemic immune responses
Author(s): Litton MJ (REPRINT) ; Dohlsten M; Hansson J; Rosendahl A; Ohlsson L; Kalland T; Andersson J; Andersson U
Corporate Source: UNIV STOCKHOLM,ARRHENIUS LABS NAT SCI, DEPT IMMUNOL/S-10691 STOCKHOLM//SWEDEN/ (REPRINT); UNIV STOCKHOLM,WENNER
GREN INST, DEPT IMMUNOL/S-11345 STOCKHOLM//SWEDEN/; LUND
UNIV,WALLENBERG LAB, DEPT TUMOR IMMUNOL/S-22101 LUND//SWEDEN/; HUDDINGE
HOSP,DEPT MICROBIOL/S-14186 HUDDINGE//SWEDEN/; HUDDINGE HOSP,DEPT
PATHOL/S-14186 HUDDINGE//SWEDEN/; HUDDINGE HOSP,DEPT INFECT DIS/S-14186
HUDDINGE//SWEDEN/; KAROLINSKA INST,ST GORANS CHILDRENS HOSP, DEPT
PEDIAT/S-11281 STOCKHOLM//SWEDEN/
Journal: AMERICAN JOURNAL OF PATHOLOGY, 1997, V150, N5 (MAY), P1607-1618
ISSN: 0002-9440 Publication date: 19970500
Publisher: AMER SOC INVESTIGATIVE PATHOLOGY, INC, 428 EAST PRESTON ST,
BALTIMORE, MD 21202-3993
Language: English Document Type: ARTICLE
Abstract: Repeated injections of a fusion protein containing the %%%superantigen%%% %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%% (SEA)
combined with a Fab fragment of a tumor-specific antibody is a highly efficient immunotherapy for mice expressing lung melanoma micrometastasis. In the present study, the systemic and local immune responses generated by this therapy were analyzed at a cellular level. Two distinct but coupled immune reactions occurred after repeated therapy. Tumor necrosis factor and macrophage inflammatory protein-1 alpha and -1 beta were immediately synthesized, in the absence of T lymphocytes, at the local tumor site in the lung. This was followed by the induction of VCAM-1 adhesion molecule expression on pulmonary vascular endothelial cells. concurrently, the early response in the spleen was characterized by the induction of selective T cells producing interleukin (IL)-2. The primed and expanded SEA-reactive V beta 3- and V beta 11-expression T lymphocytes accumulated to the tumor
area only after Fab-SEA therapy and were not present in the lung when SEA, Fab fragment, or recombinant IL-2 was injected. The tumor-infiltrating T cells produced large amounts of interferon-gamma, but no IL-2 or Th2 type of lymphokines were detected at the tumor site in the Fab-SEA-targeted anti-tumor immune response. These results emphasize the necessity to investigate several sites of antigen presentation to elucidate the effects of immunotherapy.

7/7/37 (Item 14 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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05757884 Genuine Article#: WV965 Number of References: 45
Title: Ligation of MHC class I induces apoptosis in human pre-B cell lines, in promyelocytic cell lines and in CD40-stimulated mature B cells
Author(s): WallenOhman M; Larrick JW; Carlsson R; Borrebaeck CAK (REPRINT)

Corporate Source: LUND UNIV,DEPT IMMUNOTECHNOL, POB 7031/S-22007
LUND//SWEDEN/ (REPRINT); LUND UNIV,DEPT IMMUNOTECHNOL/S-22007
LUND//SWEDEN/; PALO ALTO INST MOL MED,/MT VIEW//CA/94043; BIOINVENT INT
AB,/S-22370 LUND//SWEDEN/
Journal: INTERNATIONAL IMMUNOLOGY, 1997, V9, N4 (APR), P599-606
ISSN: 0953-8178 Publication date: 19970400
Publisher: OXFORD UNIV PRESS, WALTON ST JOURNALS DEPT, OXFORD, ENGLAND OX2
6DP
Language: English Document Type: ARTICLE
Abstract: A murine mAb (BAL-1) was previously shown to induce apoptosis when cross-linked on the cell surface of different B acute lymphocytic leukemia (ALL) and pro-myelocytic cell lines. The present study shows that BAL-1 specifically recognizes the MHC class I (MHC-I). The apoptotic response was not dependent on the epitope specificity, since other anti-MHC-I antibodies, reacting with different monomorphic determinants of the alpha chain or beta(2)-microglobulin, also induced apoptosis in these cells, However, external cross-linking of antibodies was strictly required for the apoptotic effect. Among cells originating from mature peripheral blood B cells, anti-CD40-stimulated cells were susceptible to anti-MHC-I-induced apoptosis, whereas B cells activated with %%%Staphylococcus%%% aureus Cowan I (SAC) or with the %%%superantigen%%% %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%% (SEA)
were non-responsive. Mature SEA-activated T cells were also resistant to MHC-I-induced apoptosis. In situ terminal deoxynucleotidyl transferase staining of apoptotic cells at various stages during MHC-I-induced cell death revealed that apoptosis occurred predominantly in the G(2)/M phase of the cell cycle, with the first apoptotic cells appearing after similar to 12 h of incubation. These results suggest a role for MHC-I-mediated apoptosis during differentiation and activation of certain hematopoietic cells.

7/7/38 (Item 15 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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05754771 Genuine Article#: WV761 Number of References: 33
Title: Functional characterization of the interaction between the %%%superantigen%%% %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%% and
the TCR
Author(s): Antonsson P (REPRINT) ; Wingren AG; Hansson J; Kalland T; Varga
M; Dohlsten M
Corporate Source: PHARMACIA & UPJOHN INC,LUND RES CTR, POB 724/S-22007
LUND//SWEDEN/ (REPRINT); LUND UNIV,DEPT TUMOR IMMUNOL, WALLENBERG
LAB/LUND//SWEDEN/
Journal: JOURNAL OF IMMUNOLOGY, 1997, V158, N9 (MAY 1), P4245-4251
ISSN: 0022-1767 Publication date: 19970501
Publisher: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA, MD
20814
Language: English Document Type: ARTICLE
Abstract: In this report, we show that despite an overall amino acid residue identity of more than 80% between the %%%staphylococcal%%% %%%enterotoxins%%% (SE) A and E, these proteins markedly differ in their absolute requirement for the MHC class II during T cell activation, The super-antigens were produced as C215Fab-SE fusion proteins and analyzed for their ability to activate T cells in a MHC class II-independent manner, using C215 Ag expressing cell lines as pseudo super-APCs, C215Fab-SEA, but not C215Fab-SEE, induced T cell cytotoxicity and proliferation in these MHC class II-independent systems, Introduction of a region from SEA, comprising amino acids 20-27, to SEE transferred the ability to engage T cells in the absence of MHC class II, Analysis of the V beta specificity of the chimeric SEA/SEE molecules and a panel of SEA %%%mutants%%% demonstrated that
the site for TCR interaction covers the edge surrounding the shallow cavity on top of the SEA molecule.

7/7/39 (Item 16 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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05718942 Genuine Article#: WT196 Number of References: 48
Title: Molecular characterization and role in T cell activation of %%%staphylococcal%%% %%%enterotoxin%%% %%%a%%% binding to the HLA-DR
alpha-chain
Author(s): Thibodeau J (REPRINT) ; Dohlsten M; Cloutier I; Lavoie PM; Bjork
P; Michel F; Leveille C; Mourad W; Kalland T; Sekaly RP
Corporate Source: INST PASTEUR,UNITE IMMUNOCHIM ANALYT, DEPT MOL IMMUNOL,
25 RUE DR ROUX/F-75724 PARIS 15//FRANCE/ (REPRINT); CLIN RES INST
MONTREAL,IMMUNOL LAB/MONTREAL/PQ H2W 1R7/CANADA/; MCGILL UNIV,DIV EXPT
MED/MONTREAL/PQ/CANADA/; PHARMACIA ONCOL,DEPT IMMUNOL/LUND//SWEDEN/;
INST PASTEUR,UNITE IMMUNOCHIM ANALYT, DEPT MOL IMMUNOL/F-75724 PARIS
15//FRANCE/; UNIV LAVAL,CTR HOSP, RES CTR, DEPT RHEUMATOL IMMUNOL/ST
FOY/PQ G1K 7P4/CANADA/; UNIV MONTREAL,DEPT MICROBIOL & IMMUNOL/MONTREAL/PQ H3C 3J7/CANADA/
Journal: JOURNAL OF IMMUNOLOGY, 1997, V158, N8 (APR 15), P3698-3704
ISSN: 0022-1767 Publication date: 19970415
Publisher: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA, MD
20814
Language: English Document Type: ARTICLE
Abstract: %%%Superantigens%%% bind to MHC class II-positive cells and stimulate T lymphocytes expressing specific V beta regions of the TCR. Two distinct regions of %%%staphylococcal%%% %%%enterotoxin%%% %%%A%%%
%%%superantigen%%% (SEA) have been shown to affect the binding to MHC
class II molecules. Results presented here demonstrate for the first time that the SEA-DR interaction can be affected by mutations on the class II alpha-chain. Furthermore, we have precisely mapped the interaction of the SEA N-terminal domain with the alpha 1 domain of HLA-DR. Scatchard analysis using DAP cells transfected with %%%mutant%%% class II molecules showed a role for residue DR alpha K39
in the binding of SEA. Also, complementation experiments using %%%mutant%%% SEA molecules revealed an interaction between SEA residue
F47 and position alpha Q18 on an outer loop of HLA-DR. These interactions between SEAF47 and the DR alpha-chain are critical, as they allow the recognition by an otherwise nonreactive V beta 1(+) T cell hybridoma and induction of tyrosine phosphorylation through the TCR.

7/7/40 (Item 17 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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05514742 Genuine Article#: WD562 Number of References: 43
Title: V alpha domain modulates the multiple topologies of mouse T cell receptor V beta 20/%%%staphylococcal%%% %%%enterotoxins%%% A and E
complexes
Author(s): deAlba YB (REPRINT) ; Marche PN; Cazenave PA; Cloutier I; Sekaly
RP; Thibodeau J
Corporate Source: INST PASTEUR,UNITE BIOL MOL GENE, 25 RUE DR ROUX/F-75724
PARIS 15//FRANCE/ (REPRINT); INST PASTEUR,DEPT IMMUNOL, UNITE
IMMUNOCHIM ANALYT/F-75724 PARIS//FRANCE/; UNIV PARIS 06,URA CNRS
1961/PARIS//FRANCE/; UNIV MONTREAL,INST RECH CLIN, IMMUNOL
LAB/MONTREAL/PQ/CANADA/; UNIV MONTREAL,DEPT MICROBIOL &
IMMUNOL/MONTREAL/PQ/CANADA/; MCGILL UNIV,DEPT MICROBIOL/MONTREAL/PQ H3A
2T5/CANADA/; MCGILL UNIV,DEPT IMMUNOL/MONTREAL/PQ H3A 2T5/CANADA/;
MCGILL UNIV,DEPT EXPT MED/MONTREAL/PQ H3A 2T5/CANADA/
Journal: EUROPEAN JOURNAL OF IMMUNOLOGY, 1997, V27, N1 (JAN), P92-99
ISSN: 0014-2980 Publication date: 19970100
Publisher: VCH PUBLISHERS INC, 303 NW 12TH AVE, DEERFIELD BEACH, FL
33442-1788
Language: English Document Type: ARTICLE
Abstract: The %%%superantigens%%% %%%staphylococcal%%% %%%enterotoxin%%%
%%%A%%% and E (SEA and SEE) both contact major histocompatibility complex (MHC) class II molecules on two sites located on the alpha and beta chains. We have investigated the role of the T cell receptor (TCR) alpha chain in the modulation of the various topologies of TCR/SEA (or SEE)/class II complexes. For this purpose, we have usedthree mouse V beta 20 T cell lines expressing different V alpha domains and two T cell hybridomas expressing mouse V beta 1 or V beta 11 segments. The response of these T cells to SEA and SEE was studied in the context of presentation by wild-type human MHC class II molecules; or by %%%mutants%%% on MHC,in each of the two %%%superantigen%%% binding
sites (position alpha 39K and beta81H) to which the %%%superantigens%%%
can still bind but with an altered conformation. Although V beta 20 T cell lines are efficiently stimulated using SEAand SEE presented by wild-type HLA-DR1 molecules, our results show that the nature of the TCR V alpha domain can affect differently the recognition of the toxins